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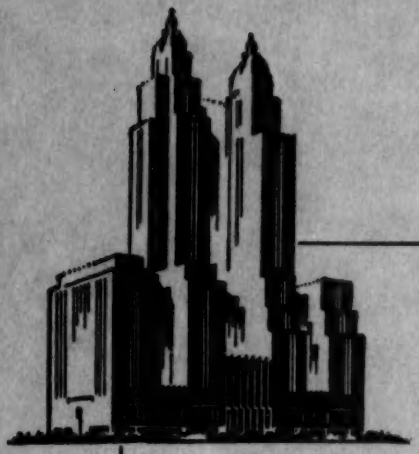

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ANNALS OF
INTERNAL MEDICINE

VOLUME 10 NOVEMBER, 1936 NUMBER 5

THE POSTURAL SYNDROME RELATED TO OBESITY LEADING TO POSTURAL EMPHYSEMA AND CARDIORESPIRATORY FAILURE*

By WM. J. KERR, M.D., F.A.C.P., and JOHN B. LAGEN, M.D.,
San Francisco, California

IT is our purpose to discuss one of the most important syndromes seen in the practice of adult medicine, and to suggest measures for symptomatic relief based upon knowledge of bodily mechanics and function. We refer especially to a type of obesity which appears to be exogenous in origin, arising in persons whose dietary habits lead to a caloric intake beyond their daily requirements. It is not easy to determine whether individuals with the relaxed habitus are predisposed to the train of events which follows, but it is apparent that when medical attention is sought these patients present the posture of relaxation. The gradual accumulation of adipose tissue in the normal depots for fat gives the appearance of rotundity, and the state is usually designated as corpulency. The accumulation of fat in the third decade is relatively symptomless. Friends will comment on the gain in weight, and subjects will note the expanding girth with the attendant strain on buttons and realize that they must discard belts for suspenders. At this stage some dyspnea will be noted on exertion, and a few suffer from symptoms referable to strain of the spinal column.

In the fourth decade the appearance of the individual is one of increasing corpulency, with a tendency toward a florid complexion. The normal curves of the spine are accentuated. The added weight of fat of the abdominal wall and viscera moves the line of gravity forward, and to compensate for this the major portion of the thorax is moved backward, accentuating the lumbar curve. The upper part of the thorax and shoulder-girdle move forward, increasing the normal thoracic curve; and the head and neck are thrust forward as is required for adjustment at a new line of gravity.

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The resulting strain on the spinal column and its mechanical devices for maintaining the erect posture is great. At this stage symptoms arise which bring the patient to the internist, the orthopedist, the neurologist, the gynecologist, and specialists in almost every branch of medicine. If treatment is directed to symptomatic relief alone, the results are rarely satisfactory and recurrences are frequent. The use of mechanical appliances and postural training does not remove the real cause of trouble which arises through the accumulation of fat with its added weight forward of the normal line of gravity. Under such circumstances, postural training can minimize the strain in some measure, but only by increasing effort as the protuberant abdomen gains in the race with the individual's ability to compensate.

The fifth decade marks the period of transition from the state of physical well-being and activity of youth to one of gradual lessening of activity of middle and old age. There frequently occurs at this time a change in the habits of living, distinguished chiefly by diminution of active exercise or even normal activity, and by increase in the consumption of food. Finally, it is at this time of life that changes occur in the body which herald the onset of presenile degenerations. These are the depositions of fat, increased flabbiness of muscles, atheromatous changes in the blood vessels and those gradual changes in skin, connective and glandular tissue which are difficult to define. These latter may be described as loss of elasticity and repairability with consequent lessened tone and poor response to injury such as strain in muscles and ligaments or pressure on bone and cartilage.

The foregoing is the fate of most individuals who live to a sufficient age; though the time of onset, the rapidity of progression and the degree of bodily change vary greatly. These normal changes are prodromal to the onset of the postural syndrome, in fact may be considered to pave the way for its development. The syndrome itself is certainly modified or delayed in susceptible individuals by proper exercise and diet. Heredity may be a factor in its development, as shown by the familial occurrence of arteriosclerosis, arthritis, premature gray hair and particularly corpulency. Environment is directly related. The condition singles out those individuals of sedentary occupation who have little facility or desire for exercise. It is also prone to attack those whose station in life is such that ease is second nature, over-indulgence in rich food is possible, and for whom press of business may limit exercise. The most obvious result is the gradual development of a heavy, pendulous abdomen, the paunch or "watermelon belly" which was at one time almost pathognomonic of the individual having reached a certain age or position in life.

Mechanics of Posture

The upright position of the human species is phylogenetically one that has been developed from the original four-footed position. The chief, if not sole, support in this new position is the spine. Its main function is that

FIG. 1. Lateral view of spine (after Piersol: Human Anatomy; Reproduced by permission of The Macmillan Co.)

of a sustaining rod which maintains the upright position of the body and carries its weight. From the first cervical down to the last lumbar, the vertebral bodies constantly increase in mass corresponding to the increase of the weight-bearing stress from above downward, as it is finally transmitted to the sacrum which latter's five segments rapidly decrease in mass from above downward (figure 1). The spine is also a balancing rod which is wedged into the pelvic ring and serves as a post of anchorage for the muscles of the back, themselves partly concerned in maintaining balance. Equilibrium maintained by the body in an upright or standing position is active and not passive, and muscular forces must constantly be engaged in opposing and neutralizing gravitational forces. Phylogenetically, attainment of the upright position by man required special development of the extensor muscles of trunk, hips, knees and ankles.

Steindler asserts, " A law of statics states that any force, if applied to a body, can be resolved into a translatory force and a so-called couple of rotating forces, the latter being so arranged that a line connecting their points of application goes through the so-called center of gravity. This center of gravity represents the one mass-point of the body which is so situated that the gravital force for all other mass-points of the body can be imagined to go through it." In man, it is located at about the level of the second sacral segment of the spine midway between the spine and a vertical prolongation of the hip-joints, in the midline. To quote again, " As long as all the partial forces of gravity apply in the center of gravity and as long as this center of gravity falls directly over the supporting surface, then the body is balanced and the resistant counterforces apply forces co-linear and in opposite direction to the gravitational force." This may be graphically represented by the line of gravity. Viewed from a frontal plane, this line of gravity bisects the body into two symmetrical halves. Viewed laterally, the line of gravity arises from the supporting surface of the feet between ball and heel, passes through the ankle- and knee-joints, runs between the hip-joint and sacrum and through the upper ventral portion of the sacro-iliac junction; then runs upward behind the bodies of the lumbar spine, intersects the spine at the lumbothoracic junction, runs slightly in front of the thoracic spine, intersects the spine again at the cervicothoracic junction, runs slightly behind the cervical vertebrae, and touches the head behind the ear at the mastoid process (figures 2 and 3).

There is an inherent tendency in the individual to maintain the center or line of gravity at a constant relation to the points of support of the body. Usually the line of gravity falls about four centimeters in front of the center of the ankle-joint. If morphological changes occur in the body which attempt to move the center of gravity forward, for instance in pregnancy or in obesity, we see that this tendency is usually counteracted by an increased plantar flexion of the foot in the ankle-joint. Naturally this applies only to a certain degree, and excess weight will finally carry the center of gravity

forward, thus forcing the knees into flexion in order to bring the line of gravity forward also.

Mechanics of Respiration

The thorax is a semi-rigid cavity entirely shut off from the outside by the structures of the neck above, by the ribs and spine on the sides, and by the diaphragm from the abdominal cavity below. The thorax contains the

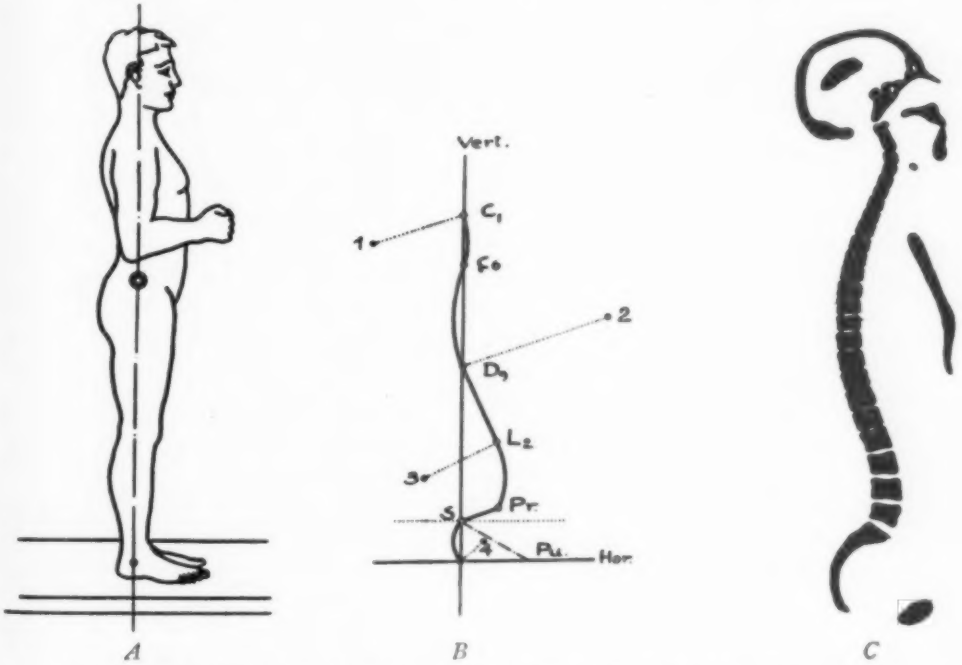


Fig. 2. Vertebral column showing curves as seen actually and in silhouette. (From Steindler's "Mechanics of Normal and Pathological Locomotion in Man"; Courtesy of Charles C. Thomas, Publisher.)
A. Normal upright posture showing line of gravity and center of gravity.
B. Intersections of the line of gravity.
C. Dorsoposterior curves.

heart, great vessels, esophagus, trachea and lungs, which latter alone interest us. The lungs may be considered as two large membranous sacs whose interior surface is multiplied greatly by subdivision into alveoli, all of which communicate freely, by gradually enlarging tubes (the bronchioles and bronchi), with the outside air. The atmospheric pressure on the alveoli expands the lungs until they fill the entire thoracic cavity not occupied by other organs, so that however the size of the thoracic cavity varies, the volume of the lungs must change accordingly. Normal respiratory movements consist of an active inspiration followed by a passive expiration, the former requiring muscular activity, the latter usually not, except during forced respirations. The amount of air that flows in and out with each normal

respiration is known as the tidal air, and averages about 500 c.c. for an adult male. The complemental air is the amount of air that can be breathed in over and above the tidal air by the deepest possible inspiration; it is about 1600 c.c. Conversely, the supplemental air is the amount that can be breathed out, after a quiet expiration, by the most forcible expiration; it is also about 1600 c.c. The vital capacity equals the tidal plus the supplemental plus the complemental air.

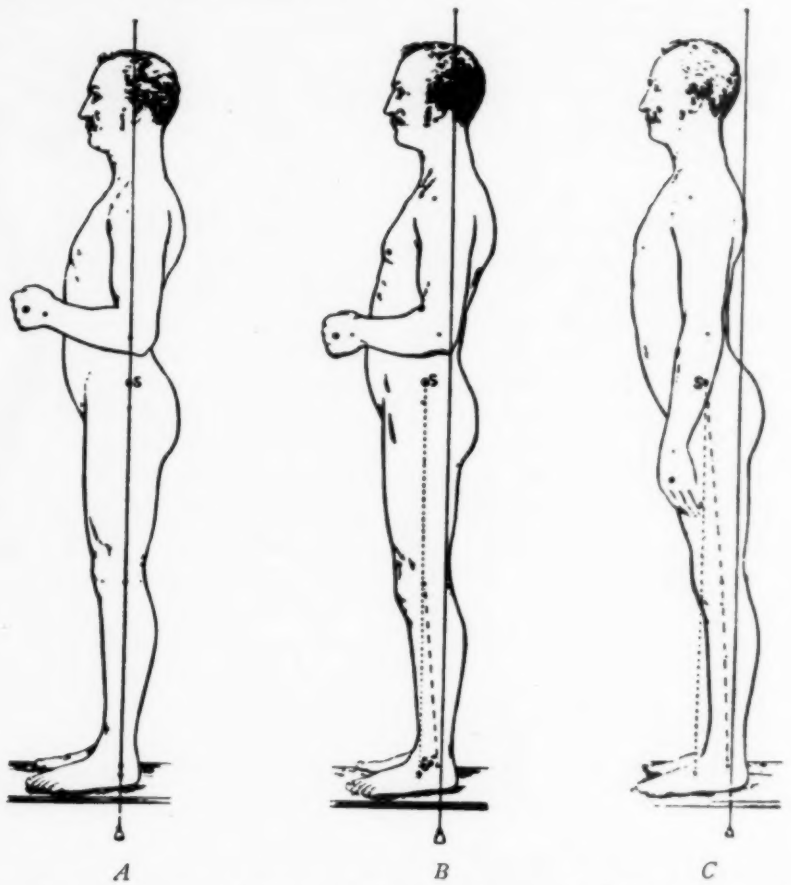


FIG. 3. Types of posture. (From Steindler's "Mechanics of Normal and Pathological Locomotion in Man"; Courtesy of Charles C. Thomas, Publisher.)
A. Normal posture.
B. Relaxed posture.
C. Military posture.

Each rib is attached to the spinal column at two points: the head to the body of the vertebra and the tubercle to the transverse process, so that up and down movements of the ribs result in a rotation around an axis joining these two points. Since the ribs slant downward to their attachment to the sternum, this with the rotation causes an enlargement in the dorsoventral

and lateral diameters of the chest every time the ribs move up, which is the act of inspiration. Therefore any muscle attached to the thorax whose contraction causes an elevation of the ribs must be considered an inspiratory muscle; and conversely, anything which elevates the ribs results in an inspiratory state of the thorax.

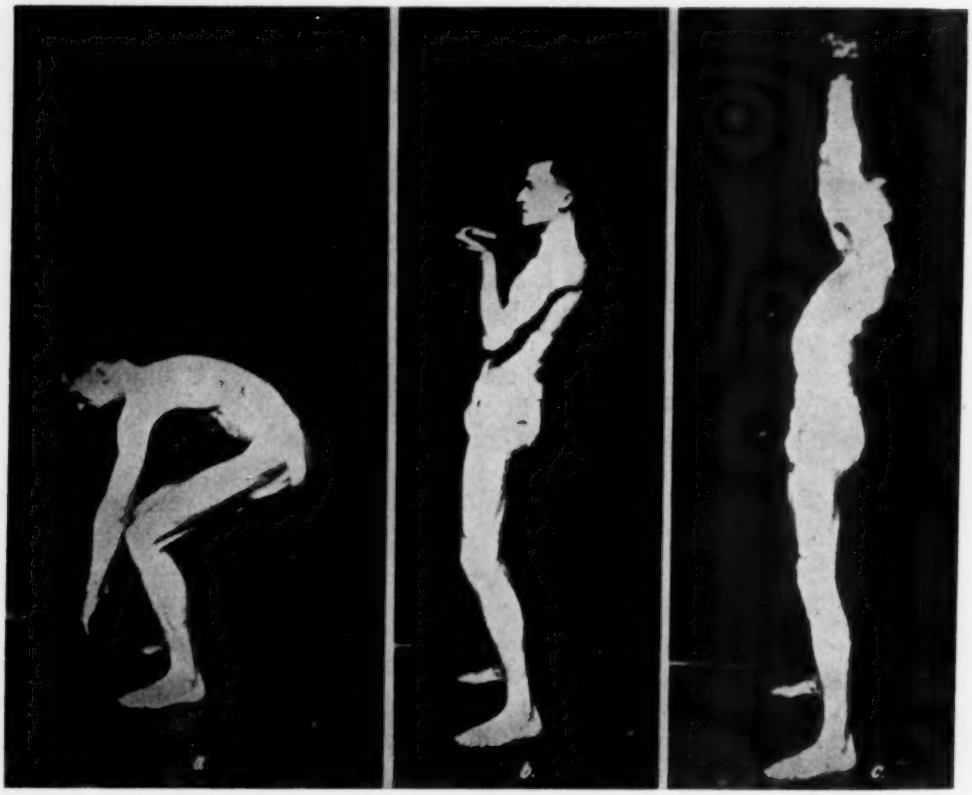
To the six lower ribs and to the xiphoid process are attached the costal and sternal portions of the diaphragm respectively; the lumbar portion attaches to the first, second, third and fourth lumbar vertebrae; and the thoracic portion to the thoracic vertebrae. From these attachments the muscular sheet extends ventrally along the walls of the thorax and then bends over to form an arch, with all the fibers inserting in the central tendon. This latter is not entirely free since the pericardium is attached to it, and may be considered as a tendinous attachment connected with the cervical fascia. A contraction of the diaphragmatic muscle draws the central tendon downward toward the abdominal cavity and therefore increases the size of the chest in the vertical diameter, while an increase in the thoracic cavity around the periphery of the diaphragm is caused also by the flattening of the muscular arch. Two results follow this movement: the lungs are expanded exactly in proportion as the cavity enlarges, which constitutes an inspiration; secondly, the descent of the diaphragm raises the pressure in the abdominal cavity, causing the abdominal wall to protrude. Expiration, as far as the diaphragm is concerned, is entirely passive, resulting from relaxation of the contraction, though aided by the abdominal pressure produced by inspiration; and still further, on forced respiration, by contraction of the abdominal musculature. Conversely again, anything which causes the diaphragm to descend results in an inspiratory stage of the thorax.

The Postural Syndrome

Description: The postural syndrome has as its basis obesity, which results in the development of a heavy dependent abdomen. It is this latter which is the obvious cause of the train of symptoms and signs that ensues. Their production depends upon two factors, unrelated except for cause, but synergic in effect. The first of these is the dragging effect exerted by the increased abdominal weight. This makes itself felt chiefly in the lumbar spine to which the weight is transmitted through muscle, fascia and skin. Here the result is at first an exaggeration of the normal lumbar curve, later an increasing lordosis with the vertebrae parting ventrally like the leaves in a book. The spine being intimately associated throughout its length, must compensate for this, which it does by causing a thoracic kyphosis and a cervical lordosis. The sacrum, normally at an angle of 45 to 60 degrees with the lumbar spine, is elevated to an angle of 90 degrees or more.

The second factor is concerned with the shift in the center of gravity produced by the excess weight which, as it were, has been attached to the front of the body. As mentioned previously, this is at first compensated for

by increased plantar flexion. When this is no longer effective, the individual is forced to compensate further, which he does by bending his knees and voluntarily increasing the lumbar lordosis through muscular action, the latter resulting also in the effect on the rest of the spine. A patient seen in lateral aspect reminds one of an individual who is attempting to " get in under " a heavy weight in order to support it more comfortably. This is somewhat



A *B* *C*

FIG. 4. External resistance: weight lifting. (From Steindler's " Mechanics of Normal and Pathological Locomotion in Man "; Courtesy of Charles C. Thomas, Publisher.)
A. From the floor.
B. To shoulder height.
C. Upward lift.
(Note the weight following closely in the line of gravity.)

similar to that which is seen in the mid-stage of lifting an external weight, as shown in figure 4. Here of course some of the weight is supported by the muscles of the arm and shoulder, and exerts a drag on the upper part of the frame also. Note the bending of the knees and the increase in normal spinal curvature.

The governing principle is that the weight to be lifted never becomes too far deflected from the line of gravity; otherwise a rotation movement will

develop which is too great to be overcome by the working muscles. With the weight in the line of gravity, the individual has only the translatory weight-stresses to overcome, and he will avail himself of the skeletal resistances for this—that is, the resistance of the rigid bones—to the best possible advantage. An analogous situation is seen in patients with abdominal obesity. Here the center of gravity has been shifted forward from the line of gravity. In order to maintain this weight with the least muscular exertion and therefore the greatest comfort, the line of gravity (which is the optimum line of weight-bearing) must be carried forward. This is done, as already stated, by bending the knees and increasing the lumbar lordosis (figure 5).

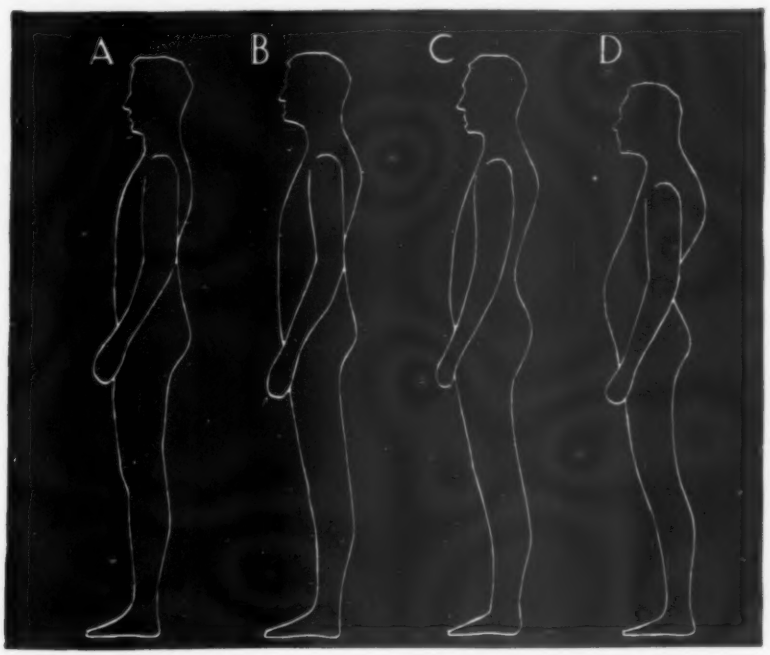


FIG. 5. **Figures illustrating good and bad bodily mechanics, based on an examination of 700 Harvard freshmen (after Lee and Brown in "The Journal of Bone and Joint Surgery"; reproduced by permission).**

Group A. 7.5%
Good mechanical use of the human body.
1. Head straight above chest, hips and feet.
2. Chest up and forward.
3. Abdomen in or flat.
4. Back, usual curves not exaggerated.

Group B. 12.5%
Fairly good mechanical use of the human body. Note changes from Group A.
1. Head too far forward.
2. Chest not so well up or forward.
3. Abdomen, very little change.
4. Back, very little change.

Group C. 55%
Bad mechanical use of the body. Note changes from Group A.
1. Head forward of chest.
2. Chest flat.
3. Abdomen relaxed and forward.
4. Back, curves are exaggerated.

Group D. 25%
Very bad mechanical use of the body. Note changes from Group A.
1. Head still farther forward.
2. Chest still flatter and farther back.
3. Abdomen completely relaxed, "slouchy."
4. Back, all curves exaggerated to the extreme.

Whichever the mode of production, the effect of the increase in lumbar lordosis is the same, resulting as it must in the compensatory increase in the other normal spinal curves. This accentuation of the curves, coupled with the bending of the knees, causes a reduction of stature. The increase in cervical lordosis forces the individual to carry his head bent forward, the degree depending upon the lordosis. To maintain the head in the normal position puts extra work on the extensor muscles of the back of the neck, so a position of comfort unconsciously results in the bowing of the head This, however, necessitates a strain on the extra-ocular muscles (recti-superior), it being easier to lift the eyes than to lift the head. Hypertrophic arthritis of the spine may be initiated, or exacerbated if already present. In particular, the radicular syndrome due to arthritis is usually made worse, or may make its first appearance when the increasing spinal curvature in the presence of the arthritis results in irritation of nerves.

The increased thoracic kyphosis is perhaps the most important effect of all in view of the result it has on respiration. This is of far-reaching importance and not limited alone to inspiration and expiration. Any increase in the normal curves of the thoracic spine, as shown by Kountz and Alexander, results in elevation of the ribs, producing thereby the barrel-chest seen typically in obstructive emphysema, but in this instance without marked emphysematous changes in the lungs. This flaring of the rib-cage also directs the lower ribs downward, which with the widening, flattens the diaphragms. Part of the mechanism that lowers the diaphragms and prevents their excursion is due to the visceroptosis.

Another significant fact is that these individuals are able to breathe with a great deal more facility when lying flat, since the relief from abdominal weight in the prone position must release the diaphragms. They suffer, not from orthopnea, but from *orthostatic dyspnea.*

There is therefore a double mechanism at work to keep the chest more or less fixed in the inspiratory phase. Consequently the tidal air is less than normal, while the complemental air is greatly reduced. Expiration may be even more affected than inspiration. There is little tendency for the chest to collapse or the diaphragm to raise at the end of inspiration; passive expiration is reduced. Expiration must now become somewhat of an active muscular exertion, and mainly thoracic since the marked visceroptosis prevents muscular exertion on the part of the abdomen to force up the diaphragm. There is not, however, the added impediment of bronchiolar narrowing as is seen in obstructive emphysema.

The reduction in pulmonary ventilation, leading to oxygen-debt on exertion particularly, results in dyspnea. This, as stated before, is orthostatic, occurring only in the upright position, but is not present on sitting or in the prone position. There is a compensation taking place, however, which is the occurrence of polycythemia in the advanced stages of the syndrome, brought on by the reduced oxygenation of the blood. This often produces

some cyanosis, or accentuates that already present. The late effects are on diminution of cardiac reserve from overstrain, constituting, in its effects on tissue-oxygenation, somewhat of a vicious cycle. Coincident arteriosclerosis complicates the clinical picture. Figure 6 shows in tabular form the inter-relationship of the syndrome.

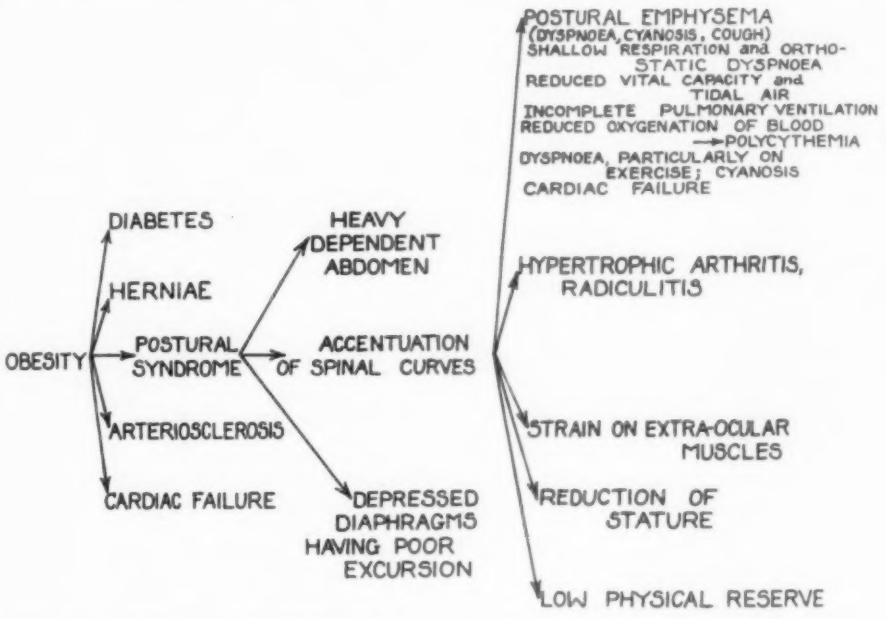


FIG. 6. Schematic representation of the postural syndrome resulting from obesity.

Symptomatology: It is during the fifth and sixth decades that patients in this group are obliged to seek medical advice from the internist. The clinical syndrome is, as a rule, remarkably complete. The presenting symptoms are usually increasing *orthostatic dyspnea,* cough, cyanosis and edema, referable to the respiratory and circulatory systems. Along with these, or as chief symptoms, are radiculitis associated with " irritation " of nerve-roots; a group of less well-defined symptoms originating in the vertebral bodies, intervertebral discs and ligaments; symptoms resulting from muscular strain and weakness, including pains in the orbits associated with strain on the extra-ocular muscles and such obvious defects as ventral and inguinal herniae; symptoms of strain on the lumbosacral and iliosacral articulations; and symptoms of strain on the hip- and knee-joints and the arches of the feet.

The physical examination may be made for the first time with the patient in bed suffering from respiratory and circulatory symptoms. In such emergencies, the full clinical picture may not be readily appreciated. The extremely florid complexion, with cyanosis, cough and edema, direct one's attention to the cardiorespiratory apparatus. The emphysematous chest

interferes with proper examination of the heart. The blood pressure is normal or slightly elevated. The abdomen is full, and a large accumulation of fat locally is often mistaken for ascites. The great protuberance of the abdomen can be appreciated only when the patient is able to stand. The kyphos in the upper thoracic spine may be so marked that such patients, while lying almost horizontal in bed, will hold the neck and head in a vertical position. The examination of the blood shows usually a hemoglobin content above 100 per cent (Sahli), and the red blood cells above 5,000,000 per c.c. Percentages of hemoglobin of 110 per cent, and red cells above 6,000,000 are not uncommon. The vital capacity at this, the late stage, is usually reduced. With proper treatment for congestive cardiac failure, the balance is soon reëstablished in most cases. It is surprising to observe the promptness with which patients are able to rest in the recumbent position, in contrast to patients with congestive cardiac failure from other causes. When these patients become ambulatory, they exhibit extreme examples of the postural defects which will now be described.

The appearance of the patient when fully undressed, and when viewed at a distance from the side is one of extreme relaxation. The most striking feature is the rounded protuberant abdomen; but upon further inspection it is apparent that the entire outline of the silhouette is altered. The curves of the spine are all accentuated; there is a moderate or marked lordosis of the lumbar spine, the sacrum is more horizontal than normal, and the thoracic spinal curve is increased with the shoulders forward and the arms suspended in front of their normal position; the upper ventral thoracic region is depressed; the head and neck are well forward with the chin out, accentuating the increasing kyphos in the upper thoracic spine; the eyes are elevated to retain vision in a horizontal direction; the pelvis is rotated backward; and the legs are flexed at the knees. The stature is shortened more or less, and sometimes patients state that they have lost two or more inches in height from their measurements earlier in life. They have the appearance of stooping to avoid an overhead obstruction. Several have remarked that their friends ask why they always stand as if they were entering a low tunnel (figure 7). They have the appearance in outline of women in the later months of pregnancy, which may be duplicated in the normal individual by holding in the hands or by suspending in front of the abdomen a heavy weight (figure 8). If such faults in the distribution of weight were not corrected by re-alignment through the shifting of other masses of the body, the individual would be unable to maintain the erect posture (figure 9).

A more detailed study of the skeletal alterations in this syndrome is of interest. The lateral roentgenograms, when taken in the position naturally assumed by the patient, show well the accentuation of the spinal curves and some of the alterations of individual vertebrae and intervertebral discs. In the two regions where lordosis is produced—namely, the lumbar and cervical segments—the vertebral bodies tend to separate at their ventral margins with

their articulating surfaces in line with radii converging at a point nearer to the spine than is normal. This is particularly striking in the lumbar vertebrae, which seem to spring apart ventrally like short leaves of a book. The intervertebral discs are wedge-shaped in appearance, filling the spaces. The

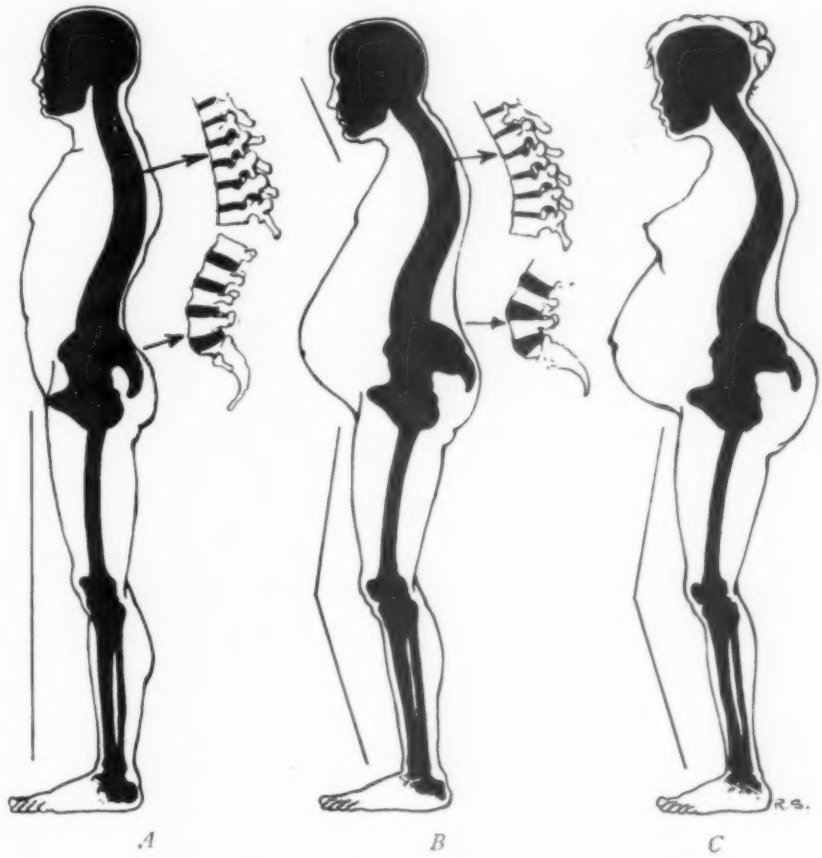


FIG. 7. Types of posture showing effects on spine.
A. Posture, spinal curves and intervertebral discs normal.
B. Relaxed posture with accentuated spinal curves resulting from a pendulous abdomen.
C. Postular changes late in pregnancy, similar to those in *B*, but which never persist long enough to affect the intervertebral discs.

lumbosacral articulation is likewise wider open ventrally than normal, and the weight-bearing surface seems to be limited to a narrow zone at the dorsal margin of the junction. The sacrum lies more horizontal than is normal; and the upper inlet of the pelvis is tilted backward and downward with the accompanying elevation of the acetabulum. The femur is inclined forward from the vertical line at its lower end, and the knee flexed slightly. In the thoracic spine the dorsal convexity is increased unless an associated ankylosing arthritis prevents this compensating movement. At some sector of the

thoracic spine the vertebral bodies tend to be compressed ventrally, and wedge-shaped; and the intervertebral discs share likewise in a similar deformity. The kyphos of the upper thoracic spine is sometimes very marked, with an appearance of the vertebral bodies resembling a crushing "jack-

FIG. 8. Lateral views of women in the late weeks of pregnancy, showing accentuated spinal curves.

knife fracture." The margins of the vertebrae and their articulations with the ribs frequently show lipping and spurs designated as hypertrophic arthritis. In the degenerative changes accompanying old age, the mechanical factors in faulty posture probably determine the location of these changes and may be more important in their causation than is generally understood.

Examination of the thorax shows some of the obvious effects of the faulty posture. In the usual posture on relaxation, the ribs stand in a more horizontal position than normal and incapable of normal elevation and expansion of the lungs. With respiratory effort, such as is made when per-

forming the test for vital capacity, the full expansion can be attained in the uncomplicated case. The diaphragms move the normal distance, or nearly so, on effort; but in ordinary breathing in the upright position it is obvious on auscultation that the expiratory phase is prolonged. The upper and

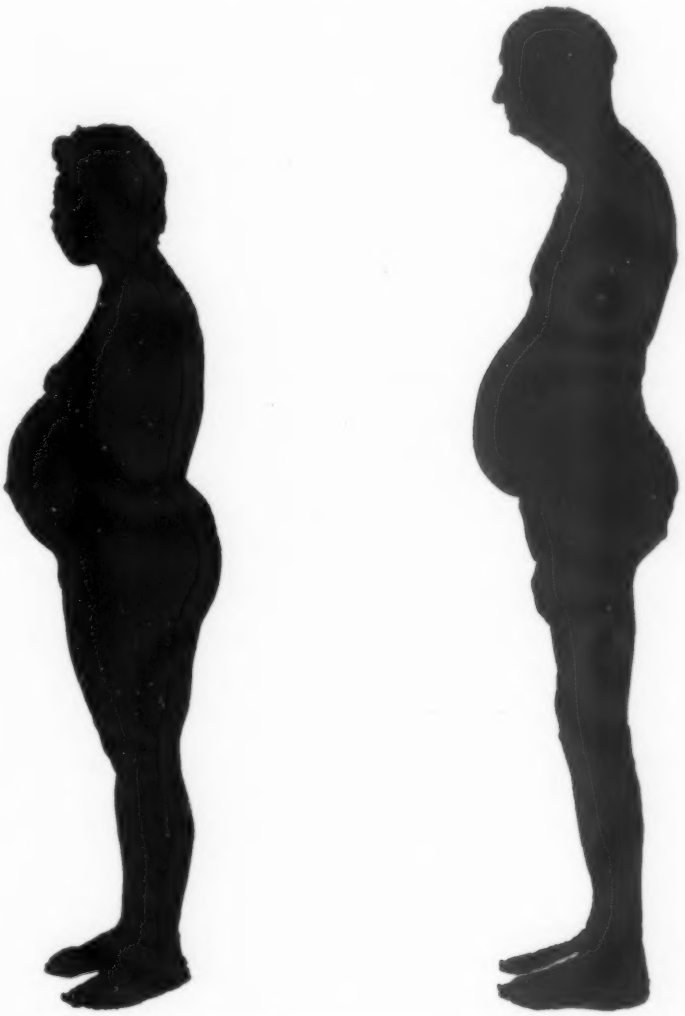


FIG. 9. Silhouettes of a woman late in pregnancy and a man with a pendulous abdomen.

ventral portions of the lungs are hyperresonant, as well as the bases behind. The veins in the neck and of the shoulder-girdle may be distended. Fluoroscopic examination of the chest usually shows little or no cardiac enlargement in the early stages, and in many cases the heart appears small. The emphysematous areas show increased illumination. The diaphragms move downward readily on forced inspiration, and it is of some interest to note

that toward the end of inspiration there appears to be a sudden acceleration of the movement, to be followed by a long and slow ascent of the diaphragm before the next inspiration (figure 10). The interference with the dia-

A

ORTHODIAGRAM OF MAXIMUM DIAPHRAGMATIC EXCURSION IN A PATIENT WITH POSTURAL EMPHYSEMA

B

ORTHODIAGRAM OF MAXIMUM DIAPHRAGMATIC EXCURSION IN A PATIENT WITH ASTHMA AND OBSTRUCTIVE EMPHYSEMA

FIG. 10. Orthodiagrams of diaphragmatic excursion (after Kountz and Alexander in "Medicine"; reproduced by permission).

phragmatic movements by the defects in posture, and the added weight of the visceral fat, combine to prevent normal aeration of the lungs. Hansson discusses the mechanical importance of good posture as follows: "The diaphragm arises from the costal cartilages, xiphoid process, transverse process of the twelve 'dorsal' vertebrae, and from ligaments of the psoas muscle. The diaphragm can only be anchored rigidly if the back is held in extension, and thus poor posture diminishes the diaphragmatic excursion. The stomach is attached to the diaphragm at the cardiac end, and the pyloric end is fixed to the body wall. The liver is partly suspended from the diaphragm, and the transverse colon, indirectly, by means of the mesocolon. A great load is, therefore, carried by the center of the diaphragm which, at least partially, is held through the right pericardium by the continuation of the

cervical fascia. This fascia is attached to the cervical spine and mastoid process. It can be understood, therefore, how flexion of the head and neck relaxes the cervical fascia, causing a ptosis of the viscera in the lower abdomen and pelvis. Thus, it is of importance to carry the chin in and the head back."

The vital capacity of the lungs early in the evolution of the syndrome is normal, but as the thorax changes shape after many years of faulty posture there is gradual reduction in vital capacity. This is, in part, due to the great mass of fat in the upper abdomen, and in part to the loss of elasticity in emphysematous areas of the lung. At first the contrast to obstructive emphysema is great, but in the terminal stage of postural emphysema the vital capacity may be markedly reduced also. Of greater importance is the tidal air of ordinary respiration. Although we have not been able to verify our impression that the tidal air is greatly reduced, because of the difficulties in getting patients to breathe without conscious effort under experimental conditions, there can be little doubt of such reduction under given circumstances. One of the striking symptoms described by such patients is dyspnea in the upright position, which we have designated as *orthostatic dyspnea*. Almost invariably, except in the terminal stages when secondary cardiorespiratory complications have arisen, such patients will be able to lie in the prone position without respiratory embarrassment. The reasons for this are obvious when the foregoing comments are recalled: the thorax is extended; the diaphragmatic attachments are now in a more fixed position; and the *abdominal counterweight* which must be lifted at great expenditure of energy in the upright position now becomes a minor encumbrance during expiration. The counterweight, through gravity, may now actually assist in the ascent of the diaphragm in expiration, and the elasticity of the lungs becomes a more effective agency in the exchange of gases. These considerations must be kept in mind in treatment, and will be reviewed later on in consideration of the management of the patient.

The respiratory and circulatory disturbances are complex and difficult to analyze. The faulty exchange of gases apparently leads to a compensatory polycythemia, which in our series is relatively constant. The facies of the patient is one of high reddish color, with variable cyanosis of the lips and cheeks depending on the stage of the complications in the thorax. The veins over the upper thorax and arms, and in the neck, are usually prominent; and sometimes the subclavian veins are mechanically compressed between the clavicles and the first rib. These latter veins may empty well when the shoulders are elevated. The heart may be small, normal or of large size, apparently depending on many factors. Here we must consider the degree and stage of emphysema and the immobility of the diaphragm interfering with the filling of the right heart; the extent of pulmonary arteriosclerosis and state of the right heart; the extent of systemic and coronary arteriosclerosis with and without hypertension; and the deformity

of the thoracic spine. The position and shape of the heart are influenced by the position and movements of the diaphragm. Electrocardiograms show more often a tendency to right axis deviation, but sometimes left axis deviation especially in patients with hypertension. Defects in the conduction system and arrhythmias may be observed in older subjects. Cardiorespiratory complications usually lead to an untimely death.

The radicular symptoms and signs are of frequent occurrence, extending over many years. They are related to the deformities of the spine, and have been previously reported in a general discussion of the subject by Gunther and Kerr, and many others. Of special interest in our patients with the postural syndrome has been the history of attacks of "lumbago," lumbosacral and sacro-iliac strain, sciatica, abdominal and thoracic crises, and "neuritis" of the cervical and occipital nerves. In some cases abdominal and pelvic operations are performed unnecessarily. About one-third of all patients referred to us for supposed cardiac pain have their symptoms on the basis of spinal disease in the thoracic region, and are relieved by correction of the postural defects. "Pseudo-angina" can be interpreted only as false diagnosis. Many patients are treated for pain of suspected cardiac origin, and are subjected to the anxiety which such an interpretation connotes, who could be restored to a comfortable and useful life. Gunther and Sampson have reported on this subject from our clinic.

The accumulation of fat in the abdominal wall is great in such subjects. The lack of proper exercise and function of the abdominal muscles results in atrophy and the weight of the mass of fat within and without the peritoneal cavity causes stretching of these damaged tissues. Herniae in the midline and at the sides of the recti abdominalis muscles, especially at their upper ends, are of common occurrence. Inguinal herniae are also frequently associated with strain on the abdominal muscles resulting from the extreme weight placed upon them at the nearly horizontal shelf which limits the protuberant abdomen just above the pubis.

The association of arteriosclerosis and diabetes with the postural syndrome may be related to obesity or other causes. However, these conditions frequently complicate the clinical problem and must be dealt with in treatment. Pulmonary arteriosclerosis is sometimes an added burden to an already overworked cardiorespiratory apparatus.

Diagnosis and Differential Diagnosis: The diagnosis of the postural syndrome described is usually not difficult. In the relatively symptomless period subjects show a tendency to increasing weight with emphasis on expanding girth. The compensatory changes in the spinal curves are remarked. Episodes of thoracic and abdominal crises and "attacks" of spinal origin designated as neuritis, sciatica, "lumbago," lumbosacral or sacro-iliac strain often cause the patient to consult the orthopedist, neurologist and gynecologist and less frequently the internist. The "spinal adjustor" sees many of these patients, also, and frequently after relief is not forthcoming from general practitioners and specialists.

The respiratory symptoms and signs are minimal in these early stages. There may be slight dyspnea on exertion but it is usually attributed by the patient to his gain in weight. Orthostatic dyspnea has not become marked.

With advancing years the effects upon the respiratory apparatus assume greater prominence and the evidences of strain upon structures supporting the deformed body in the upright position manifest themselves. The increasing distortion of the abdomen and the exaggeration of the spinal curves are obvious. The orthostatic dyspnea becomes pronounced. The patient shows a high color and frequently presents a slight polycythemia. The vital capacity is reduced slightly but the tidal air is apparently greatly reduced only in the upright posture. The symptoms and signs of radiculitis are often marked. The roentgenographic evidence of abnormalities in the spinal axis usually confirms and helps to explain the radicular manifestations.

In differential diagnosis we must consider obstructive emphysema and other pulmonary diseases; cardiovascular disease, especially generalized, and pulmonary arteriosclerosis which may be present in older subjects; and spinal disease leading to deformities and radicular symptoms. With advancing years it is not always easy to disentangle all the complicating factors which give rise to confusion in diagnosis.

Treatment: Prophylactic treatment would, of course, be most rational. Unfortunately, those who have a tendency to exogenous obesity (those who could personally do something about it) disregard the laws of the conservation of energy through ignorance or neglect. Sedentary habits and overindulgence in food are sure guides to obesity for a great majority of people approaching middle life. The automobile and other means for conserving energy are making the individual more toad-like. Attention to the diet and exercise will benefit the great majority of those who are approaching middle age. The cultivation of the postural reflexes will also be helpful for those with relaxed habitus.

It is unfortunate that those who manifest symptoms first in relation to spinal strain are treated improperly from a mechanical viewpoint. There may be justification for the use of casts, braces, strapping and other mechanical devices to carry the patient over the acute crisis; but, when this episode has subsided, other measures must be instituted to prevent their recurrence or the more serious results which develop through the coming years. The postural training and exercises, of which Goldthwait has been such an able exponent in this country, may be very helpful in overcoming the postural defects. They may postpone or minimize future complications. Support for the abdomen may likewise tend to restore the normal distribution of weight and line of gravity, but these measures are only makeshifts for the obese patient. There can be no real substitute for the removal of excess weight by whatever means are possible, but chiefly through restrictions in diet and increased exercise. When all these measures are combined

we can offer the best plan for restoration of normal function. Without reduction of weight and especially of the abdominal region, we are frustrated in our efforts to secure the best results.

In the treatment of our patients, mostly males in the fifth and sixth decades, most of whom have appeared in the later stages of the syndrome, we have been confronted with symptoms of marked severity. However, those with less marked symptoms have responded well to the same measures. The point of attack is in three directions, but with the same end in view:

1. Temporary elastic support of the pendulous abdomen.
2. Reduction in weight.
3. Postural exercises.

1. *Elastic Abdominal Support:* * It occurred to one of us that if the patient could be given an abdominal support to overcome some of the weight applied to the diaphragm during inspiration and to relieve the *counter-weight* during expiration, the tidal air would be greatly increased; the spinal curves would be straightened; and the line of gravity moved backward. If a belt were devised which gave abdominal support and if elastic materials were inserted in the belt at the sides of the abdomen, the tidal air could be further enhanced. These elastic materials would in effect serve as a method of giving the patient artificial respiration by assisting in the expulsion of gases from the lungs. The description of this belt is given, and view of the belt in position in figure 11.

Many belts have been devised and are used routinely for abdominal support. Their main purpose is to correct either obesity or ptosis of the abdomen by lifting and holding in the abdominal wall. They accomplish this by supplementing or replacing the abdominal musculature which has either lost its tone or, more usually, has become flabby and no longer functions properly. These belts are constructed in many ways, but all have similar materials and serve the same purpose. We have a collection of inadequate belts donated by patients, and these show great variation in type.

The belt that we are presenting embodies several new principles. As a whole it is not unusual, or very different from the many we have seen. However, it is constructed with the physiological function of the abdominal wall in mind, and is designed to supplement and aid the ventral muscles rather than to replace them. A tightly wound cloth binder would support the abdomen more efficiently but would not permit mobility necessary for respiration.

Figure 11 *C* shows the belt in place on a patient. Figure 11 *B* shows some of the details of construction. The supporter is made of coutil, pekin-stripe cloth and elastic goring; it is fastened on by stake-buckles and hooks.

The front sections and the back section are of double thickness. The outer layer is of high quality coutil, the inner of pekin-stripe cloth. The only difference between the two is in the softer and finer quality of the pekin-stripe material which, being next to the skin, prevents chafing. Both sections are tailored, or fashioned. There

* These belts have been made for us by the C. H. Hittenberger Co., 1103 Market St., San Francisco. We wish to express our appreciation to this firm for helpful criticism in the original designing of the belt, and for their courtesy and care in fitting our patients.

are three double stays in the back section with a seam at each, which permits fashioning the supporter to fit the contours of the individual patient. The back section is 8½ inches in height, and the stays are of whalebone. For conditions of extreme lordosis, the cloth section in back may be extended up to the twelfth thoracic vertebra, and have incorporated in its firm duraluminum or steel stays. The stays should not, however, be bent to fit the curve of the lumbar spine but should touch the body at only the upper and lower edges of the belt, allowing the middle to span or bridge the lordosed spine.

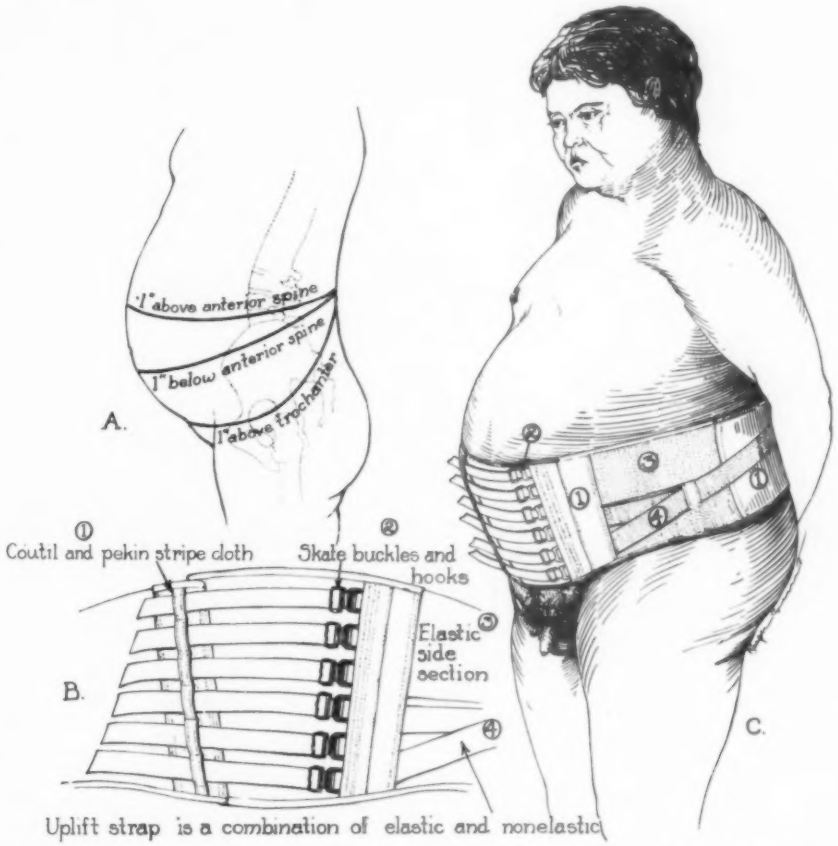


FIG. 11. Showing the details of the belt suggested for the treatment of obesity and postural emphysema, and the locations for measurements to be used in the construction of the belt.

The left front section (figure 11 $C(1)$) has the hooks attached to it. The right front section (figure 11 $B(1)$) has attached to it the straps carrying the buckles. The height of the front from top to bottom varies somewhat according to the circumference. For patients 38 inches in circumference at the crest of the ilium, a height of 9 inches is usually most satisfactory; if the patient is exceptionally tall a front height of 10 inches can be used to advantage; for patients of a circumference of 44 inches or more, a height of 10 to 12 inches is usually required. The left front section extends across the abdomen as a flap 6 inches long, padded between the two layers with strips of daisy-cloth. This provides a soft base for the straps to lie on. The width of each half of the cloth section across the front is considerably less than in the

usual supporter, being an average of 2½ inches wide. The total width of the non-elastic front is about 5 to 7 inches, but this varies with the tightness of the belt. The front flap slips under the right side of the belt as it is tightened.

The elastic lateral sections (figure 11 *C*(3)) each are made of two pieces of firm elastic goring 6 inches wide and approximately 7 inches long, placed one above the other. The two pieces overlap about 2 inches in the center, which gives greater support to the front center. The lower piece of goring on either side is set diagonally downward towards the front, exerting therefore an upward lift rather than a straight posterior pull.

The uplift strap (figure 11 *C*(4)) is a combination of elastic and non-elastic material. The front forked section consists of firm elastic webbing 1½ inches wide. The latter extends to a buckle located toward the top of the supporter just back of the hips, allowing tightening or loosening of the strap as desired. The uplift straps, being placed diagonally, exert a supporting rather than a suppressing pressure on the lower abdomen.

The belt is fastened in front by means of six skate-buckles and hooks (figure 11 *B*(2)). The buckles are slipped over the hooks with the straps loose; each may then be individually tightened to the desired degree. The extra length of strap is held up by slots at the origin, rather than allowed to dangle.

Figure 11 *A* shows the measurements required in making up a belt when the patient is not able to be fitted personally. The measurement for the upper edge of the belt is taken around the body about 1 inch above the anterosuperior spine of the ilium. The measurement for the middle of the belt should pass over the largest part of the abdomen. The measurement for the lower edge should follow the lowest line of the abdomen in front, and cross the spine in back three or four inches below the upper measurement.

The dimensions of a size-40 belt are approximately as follows:

1. *Back:* 16½ inches long at the top and 18 inches at the bottom, with three double pieces of whalebone 4½ inches apart. Height is 8½ inches.

2. *Elastic side-sections:* 6 inches long, made of two pieces of goring 5 inches wide with 2½ inches' overlap, giving a height of 8 inches.

3. *Uplift strap,* the elastic arising at the bottom in front: 5 inches long, continued by a web-strap 6½ inches long, passing through a tightening-buckle and inserted into the beginning of the back-piece 2 inches below the top.

4. *Front sections:* 2½ inches wide and 9½ inches high, the tongue 6 inches long.

It should be stated that these measurements do not designate the contouring necessary for proper fitting to the body; nor do they take into account the extra length required for seams, etc. They were taken from a finished product, laid flat.

Patients are taught to apply the belt before arising in the morning, preferably outside the undershirt. If a union-suit is worn, the belt can be worn underneath it over a thin garment. The patient should be in the supine position when putting on the belt, and the belt should be tightened from below upward. This is important in order to move the abdominal fat and viscera upward, rather than to compress it in the lower abdomen.

The unusual feature of the belt is the width and height of the elastic side-sections, particularly the width. This is obtained by making the front narrow, permitting the elastic side-sections to extend farther forward on the abdomen where the elasticity is much more beneficial than if it were placed toward the back. This increased elasticity permits expansion of the belt during inspiration. This aids, rather than suppresses abdominal breathing, and prevents limiting respiration to the thorax, as is seen in obese states naturally or where a firm, inelastic belt is applied. The increased elasticity also aids in expiration, and overcomes the prolonged expiratory period seen in those patients with depressed diaphragms due to abdominal ptosis or

emphysema. The diaphragm more readily assumes the expiratory position, and is ready to descend with the next inspiration. There is no decrease in the supportive effect during the inspiratory expansion.

Other devices which provide support plus elastic pressure during expiration would serve the same purpose. We have used belts made by inserting the elastic materials over the entire abdomen and back, with firmer materials at the sides with almost equal success. Such belts in our opinion are more beneficial for relief of symptoms in obstructive emphysema than firm belts of the type used for visceroptosis.

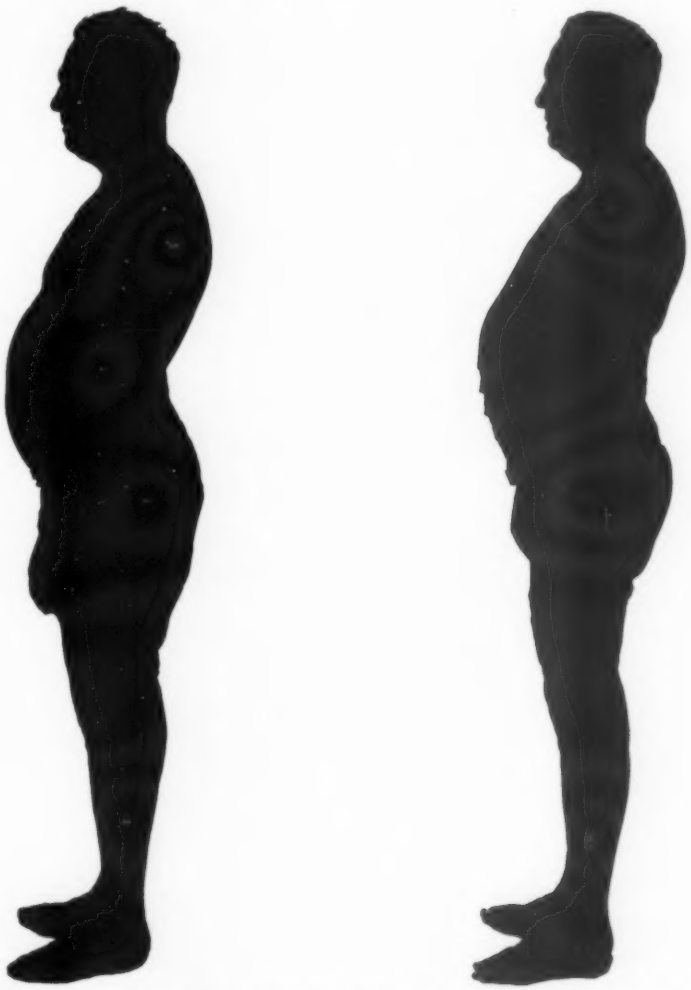


FIG. 12. Postural correction by use of the belt described. Figure on left shows position of extreme relaxation before application of belt.

It has been our experience that patients who wear the belt when up and about are obliged to stand more erect; they breathe more freely, and are

relieved of orthostatic dyspnea. They may complain of some fullness after meals which can be controlled by loosening the upper straps. However, the belt may indirectly limit the desire to eat to excess although this is not suggested to the patient, advisedly. Since most of the patients are males we have refrained from using the term "corset" to designate this belt. The

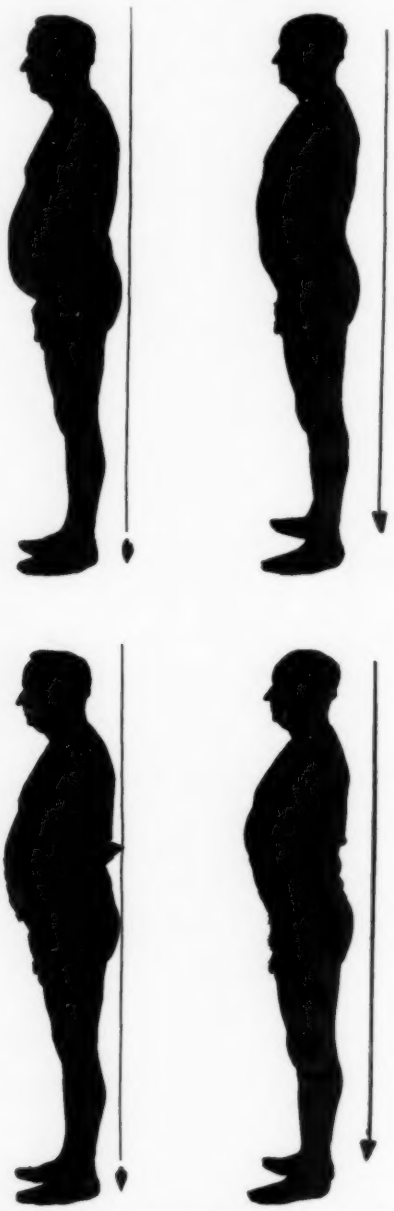


FIG. 13. Upper figures without belt, lower with belt. Left-hand figures made on first visit of patient, right-hand figures taken three months later. It should be emphasized that these are natural poses; no attempt made by the patient to exaggerate his posture.

continued use of the belt is perhaps helpful in removal of fat from the abdominal wall by continuous massage during respiration. Long continued use of the belt may weaken the abdominal muscles, but this result may be minimized by exercises which will be discussed later (figures 12 and 13).

We have observed that the color of patients improves promptly upon use of the belt. The brilliant color associated with the polycythemia diminishes, and cyanosis of the mucous membranes and nails is less striking. We have not followed a large enough series of patients long enough to secure accurate controls of the degree of polycythemia after treatment.

2. *Reduction in Weight:* The plan for reduction in weight must be individualized for each patient, depending upon occupation, opportunity for exercise and general physical condition. A caloric intake should be determined which may be as low as 800 to 1000 calories for some patients. At first two or three pounds per week may be lost and later not more than one or two pounds per week until the patient approaches the ideal weight after a period of six months. In some of these patients the problem of dietary intake is a difficult one, as all who have treated obesity can testify. For the great majority, however, the severity of their previous disability, and the remarkable relief derived by use of the belt give them confidence in measures directed toward the source of their trouble. A silhouette of themselves from the side before treatment will often be a great stimulus for coöperation. The lessening of the girth due to loss of fat and improved posture will also lend encouragement.

3. *Postural Exercises:* Chief among the postural exercises are those which educate the patient to stand properly until the postural reflexes assume command. This requires attention toward the correction of the position of relaxation. Patients should periodically stand with their backs to the wall touching the wall at as many points as possible. When some of the excess weight has been removed, the abdominal muscles may be strengthened by graduated exercises. The familiar admonition to " suck up the guts " employed by instructors in physical education may be very easy to accomplish by boys in their early years, but is almost impossible for the obese.

Summary

The postural syndrome which begins with obesity in the relaxed type of individual and passes through a series of events with increasing protuberance of the abdomen and deformity of the spine, is discussed. The results of continued strain on the spinal axis and irritation of the spinal nerves are manifested by diverse clinical symptoms and signs which frequently bring the patient to specialists in many branches of medicine. The later complications in the abdominal wall, such as herniae, may be classed as " blow-outs " resulting from weakness of the retaining structures. The respiratory and circulatory manifestations are primarily due to interference with proper ventila-

tion of the lungs based upon postural defects and the disadvantages under which the diaphragm functions under the circumstances. The orthostatic dyspnea, reduced vital capacity and tidal air, polycythemia and cyanosis are closely related. In older subjects hypertension, systemic and pulmonary, and arteriosclerosis account for definite cardiac complications. Treatment requires temporary support for the pendulous abdomen and assistance in the evacuation of the lungs during expiration. A belt which gives this support and aids in expiration through the elastic force of materials inserted in the sides of the belt, is described. This we have found of great benefit in the early months of treatment. The weight should be gradually reduced to correct the distortion of the spinal axis and restore the spinal curvature. Postural training is of greater value after the adipose tissue has been reduced, but is of little value in the patient with a pendulous abdomen and a great counterweight of visceral fat which interferes with the ascent of the diaphragm during expiration.

Conclusions

The postural syndrome beginning with obesity leading to postural pulmonary emphysema and spinal-curve distortion is described, and measures are suggested for treatment which, in our hands, have been of value.

We wish to express our appreciation to Dr. John B. DeC. M. Saunders for his suggestions and helpful criticisms.

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EMPHYSEMA: REBREATHING, BASAL METABOLIC RATE DETERMINATIONS, VITAL CAPACITY *

By Henry M. Thomas, Jr., M.D., F.A.C.P., *Baltimore, Maryland*

The classical picture of pulmonary emphysema is accepted without question by physicians, pathologists and roentgenologists. The chest is barrel-shaped and remains in the position of inspiration—moves as a whole—with diminished expansion and calls into play the accessory muscles of respiration. The percussion note is hyperresonant with obliteration of the compensatory spaces and the breath sounds are soft and expiration prolonged and sighing. The descent of the bases may be diminished, abdominal breathing is increased, although in long, narrow-chested individuals the diaphragms may descend freely. The lungs at autopsy are pale and voluminous, do not collapse on standing and microscopically present dilated alveoli and infundibular passages, the walls of which are often ruptured, forming unusually large bullae. The elastic tissue of the lungs is broken and the smooth muscle of the bronchioles and air passages degenerated. There is often accompanying chronic inflammatory reaction with formation of fibrous tissue, and some writers even consider pulmonary fibrosis the forerunner and constant companion of pulmonary emphysema.

Until the etiologic factors are more clearly determined pure pulmonary emphysema (not acute, or compensatory, or senile) will remain a theoretical condition and will differ with each hypothesis. There is, for instance, the large school of thought which considers changes in the chest wall and spinal column responsible for the changes in the lung known as emphysema. Another, perhaps larger, school looks on the changes in the chest wall as secondary to the lung changes and caused by the effort, doomed to failure, to compensate by over distention for the innate inadequacy of the lung tissue. A third school [1] attempts to differentiate between two types of emphysema: (*a*) that which occurs from changes in the chest wall—*postural emphysema;* and (*b*) that which occurs from some form of bronchial obstruction—*obstructive emphysema.* The postural type—actually one form of senile emphysema—is associated with little or no impairment of respiratory function, since abdominal breathing manages to expand the lungs by increased diaphragmatic expansion and compensates for the functional disability of the chest wall. Obstructive emphysema is accompanied by dyspnea, often extreme, and it has recently been shown [2] that difficulty in breathing is exaggerated by imperfect use of the respiratory muscles and great improvement can be brought about by suitable muscle training.

We have remaining, then, after eliminating acute, compensatory, senile

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From the Medical Department of the Johns Hopkins Hospital.

and postural emphysema, a small group of cases of true emphysema of the so-called obstructive type. These occur frequently as a result of asthma or pulmonary fibrosis with or without bronchitis and almost always after long continued coughing. It will not profit us to discuss whether inspiratory or expiratory obstruction is important; or whether repeated localized infections cause compensatory emphysema elsewhere in the lung,[3] which may become permanent; or whether hereditary tendency to degeneration of the pulmonary stroma is necessary. These and other points must be established if emphysema is to be prevented, but that time is not yet.

Now, although the clinical picture of emphysema, as I have said, seems to be clear and definite and is accepted as a matter of course, there actually exists much difficulty in ascertaining whether we are dealing with lungs which are merely hyper-resonant and distended but functionally efficient (postural), or whether true functional and pathologic (obstructive) emphysema exists. The fluoroscopic and roentgenographic criteria of emphysema fail in the same manner as do physical signs to provide reliable information, although the careful studies of Fray [4] have improved this method of examination. With McCann, he has shown that measurements on the roentgen-ray film of the total area of the fully expanded chest when multiplied by the anteroposterior diameter of the patient's chest provides a figure which correlates excellently with total capacity of the lungs in normal young adults. By this method the expected vital capacity of an individual can be estimated and thus a calculated normal established.

The chemical changes which accompany emphysema are well known and recently have been carefully surveyed by McCann et al.[5] These changes are thought by inference to be brought about by poor mixing of alveolar air and diminished and defective alveolar surface. The alveolar CO_2 is increased and the arterial CO_2 content is increased, the arterial oxygen content is reduced and there is an increased tolerance for high CO_2 tension in respired air.

The total lung volume, as estimated by Christie's [6] oxygen dilution method, remains essentially unchanged, but vital capacity is reduced at the expense of complemental air and residual air is increased. McCann [7] finds that when residual air is over 40 per cent of total capacity some degree of anoxemia exists and anoxemia increases more or less proportionally to the increase in the residual air. It has been assumed that an increase in residual air and decrease in vital capacity cause inefficient alveolar ventilation, which in turn leads to diminished oxygen saturation of the arterial blood. Either of these estimations (i.e., residual air or oxygen unsaturation of arterial blood) is closely correlated with dyspnea and is thought to afford a fair index of pulmonary efficiency. It seems clear, however, that neither one expresses an accurate measure of potential pulmonary efficiency for any given individual.

The elastic recoil of the lung is lost or impaired as shown by its failure

to collapse on opening the chest at autopsy and by reduction during life of the negative intrapleural pressure (Christie [8]). It has been suggested [9] that the principal factor in the loss of power to recoil is not damage to the elastic tissue of the lung but is reduction of the surface tension of the layer of moisture lining the overdistended alveoli. Correlation of loss of elastic recoil of the lung with functional respiratory impairment obviously is not available for clinical purposes.

The symptoms produced by emphysema are usually thought of as those caused by deficient oxygenation of the blood during its passage through the lung and are mainly dyspnea and cyanosis with late cardiac manifestations and occasionally secondary polycythemia.

In the course of subjecting a patient suspected of having angina pectoris to the rebreathing test devised by Baker [10] I was struck by the amount of dyspnea and cyanosis produced in the patient at the end of two minutes, whereas an average individual can continue the test for five to seven minutes with little or no discomfort. The test consists of partially filling a Benedict-Roth metabolism apparatus with room air, leaving the soda lime in the apparatus as usual, and allowing the patient to rebreathe into the closed system, thereby gradually removing the oxygen and providing a steadily lessening oxygen mixture, thus producing an increasing anoxemia. Patients with angina pectoris usually experience cardiac pain in the course of four to six minutes, but rarely complain of dyspnea. The patient was a man of 40 years whose complaint was substernal distress and dyspnea on exertion. There were no signs of cardiac failure except dyspnea on exertion and he had the classical physical findings of pulmonary emphysema. After the patient had returned to Florida it was borne in on me that this test might be used as a gauge of functional respiratory reserve. Since that time I have tested by this method 18 other cases that presented various degrees of clinical emphysema, but in no other case has there been any evidence of increased susceptibility to reduced oxygen tension. I am at a loss to explain its occurrence in the first individual. It seems possible that the increased residual air which is present in cases of emphysema contains more total oxygen than exists in normal residual air and thus allows the rebreathing test to continue for an abnormally long time before producing noticeable dyspnea or cyanosis. In any event rebreathing air in which the percentage of oxygen is constantly being reduced does not offer a means of diagnosing and measuring functional impairment of the lungs in emphysema.

Observations on the basal metabolic rate were made in the usual manner by filling the cylinder once with oxygen and once also with room air. It is interesting to note that there was no appreciable difference in withdrawal of oxygen from the closed system whether offered in room air or in a mixture approximating pure oxygen (figure 1). One may surmise from this observation that the usual method of determining the basal metabolic rate in patients with emphysema is accurate and not vitiated by the existence of

oxygen unsaturation of the arterial blood which is known to exist. Here again the large amount of residual air probably acts as a buffer to prevent unusually rapid absorption of oxygen. Actual observations on arterial oxygen unsaturation before and after each method are necessary to afford

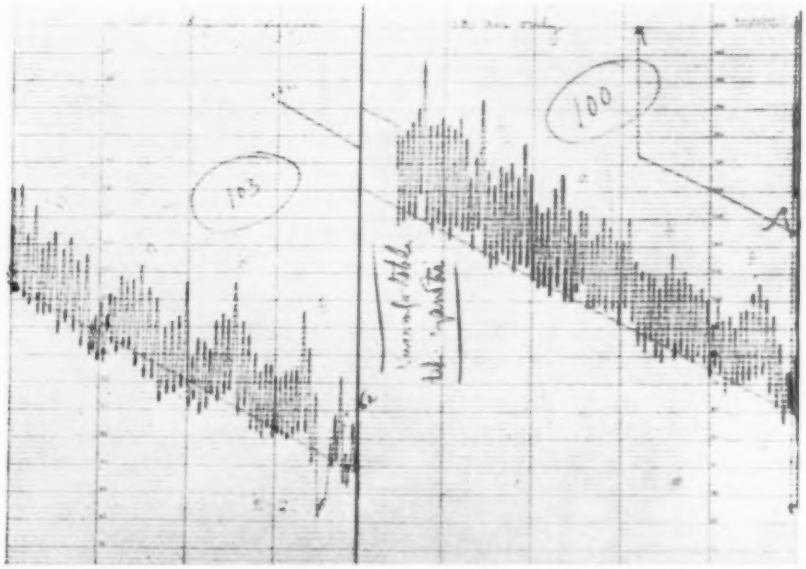

FIG. 1. Rebreathing test on a patient with advanced emphysema. The first curve represents the amount of oxygen withdrawn from room air and the second curve the amount withdrawn from pure oxygen, approximately an equal amount.

conclusive evidence on this point and these were made in only one case which showed the characteristic changes.

Finally the graphic method of recording vital capacity was added to these observations and certain variations from the normal curves were noted. In using the Benedict-Roth apparatus 20.73 c.c. of gas will raise the spirometer bell 1 mm. and the vital capacity may easily be determined by measuring on the graph in millimeters the extent of deep inspiration and forced expiration and multiplying this figure by 20.73. This method also allows vital capacity to be divided into reserve, tidal and complemental air. Without exception the vital capacity of patients suffering from clinical emphysema is reduced.

Christie has pointed out that after deep inspiration patients with emphysema are unable to blow out as much reserve air as they can after a normal inspiration (figure 2). McCann confirmed this finding in some cases but not in others, and reproduced a curve from one patient in whom the complemental air was greatly reduced and the reserve air normal or increased. A factor which seems to have been overlooked in this test is the amount of CO_2 which is absorbed by soda lime during expiration. Following inspiration after the dead space (150 c.c. to 200 c.c.) has been washed

out the expired air contains 6 to 7 per cent of CO_2, all of which is removed from the gas in the metabolism apparatus by the soda lime, causing a false lessening of the vital capacity and this false lessening appears on the graph as a shortening of the end of the downward arm which usually registers re-

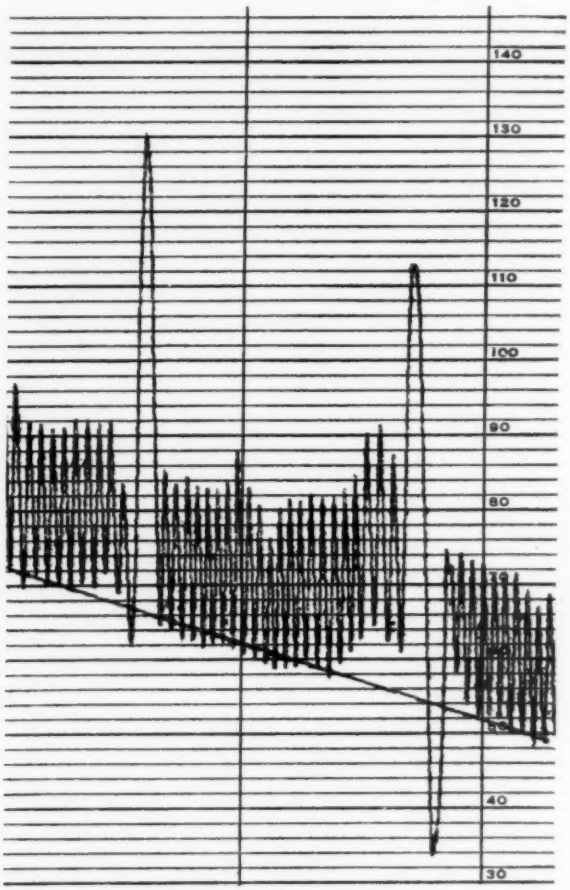

FIG. 2. Patient with moderate emphysema. Curve represents reduction in vital capacity and inability to exhale reserve air following deep inspiration.

serve air. This lessening occurs in normal individuals also. The true figure for vital capacity is more nearly approximated by starting with forced expiration after a normal inspiration and then measuring the amount of air inhaled by forced inspiration (figure 3).

From my tracings it was also noted that when breathing normally after a deep inspiration the former resting phase was reached only after 8 to 20 breaths (figure 3). I believe both of these changes are due to inefficient use of the chest wall and faulty habits of breathing rather than to the loss of pulmonary elasticity as has been previously hypothecated.

There is no reason to believe that the lung would shrink further from a partially distended state than it would from a fully distended one. Expiration is a passive movement during quiet breathing and becomes active only during dyspneic breathing. In a normal person, with normal chest wall-

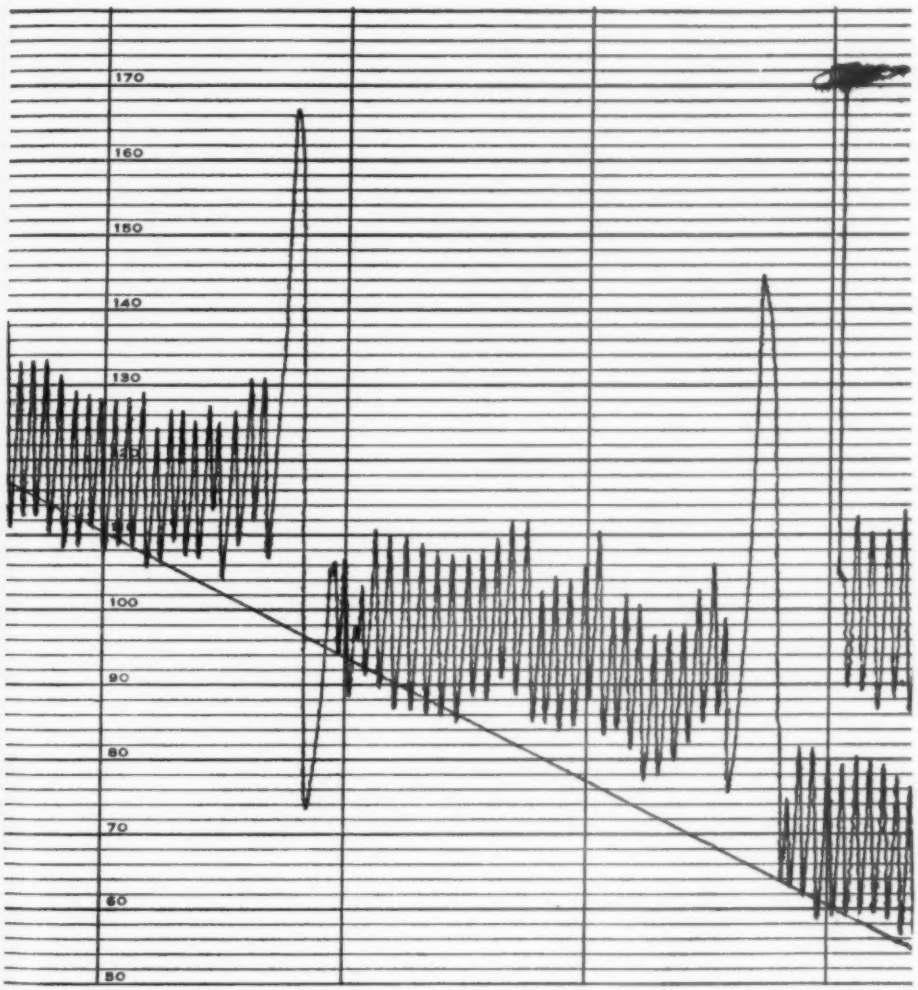

FIG. 3. Patient with extreme emphysema. Vital capacity is greater when test is begun with expiration. Former resting point is slowly regained after forced inspiration.

lung breathing mechanism, need for greater respiratory activity is supplied by more rapid ventilation of a normal or temporarily slightly increased residual air. This is done by larger inspiratory movement followed by an associated active expiratory movement with the result that the proportion of tidal air to residual air is increased. In other words, the life long habit of response to the need for more rapid ventilation of the lungs is an increased inspiratory effort with only a secondarily increased expiratory effort.

When, for whatever reason, residual air is permanently increased as it is in emphysema, tidal air is constantly increased to maintain the required residual air/tidal air proportion. This increase in tidal air on top, as it were, of an increased residual air encroaches on complemental air and brings about breathing at a higher and less efficient resting point. The larger residual

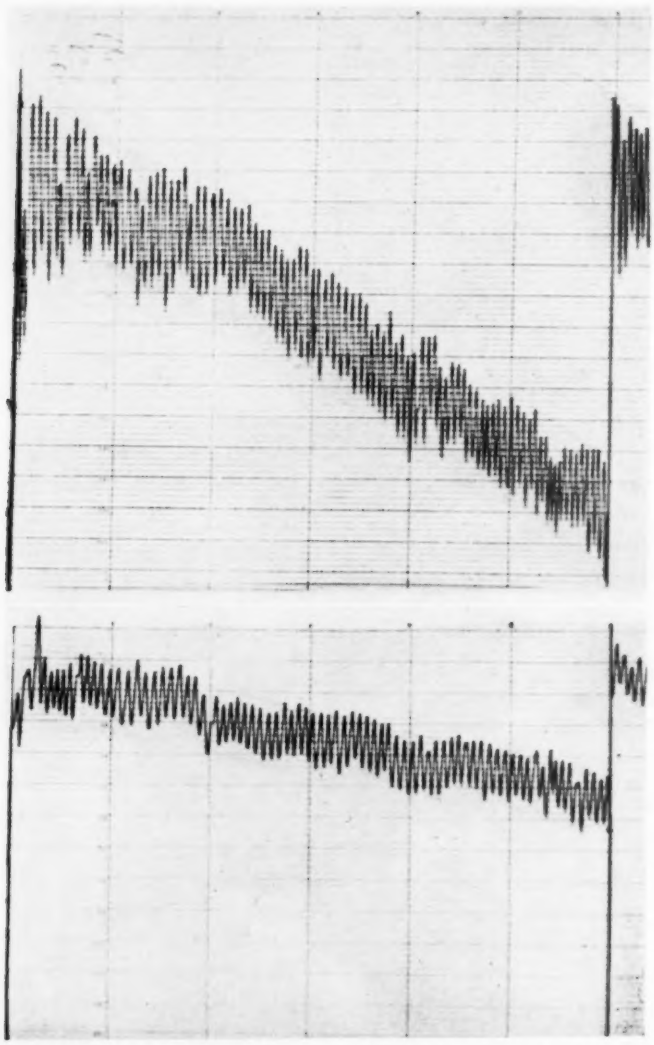

FIG. 4. Basal metabolic rate determinations before (above) and after (below) subtotal thyroidectomy. Respiratory rate is practically the same in the two tests whereas tidal air is increased in the hyper- and decreased in the hypothyroid state.

air could be more rapidly ventilated when need be if tidal air could be increased partially at the expense of residual air but the life long unconscious training of forced breathing is in the direction of voluntarily increasing

inspiration and allowing expiration automatically to keep pace. In patients with emphysema the act of forced expiration is unable to keep pace with forced inspiration as is seen in figures 2 and 3. Reserve air can be expired only when forced expiration starts from the top of tidal air, that is, from the end of a normal unforced inspiration. For this reason in our clinic we are training emphysema patients to start the respiratory cycle with forced expiration and to allow inspiration to take care of itself. It is too early to report the results of this practice but temporarily improved breathing has been noted.

Studies of tracings made during basal metabolic rate determinations of patients before and after treatment for hyperthyroidism (figure 4) in individuals possessing a normal respiratory apparatus reveal that tidal air is increased in the hyper- and reduced in the hypothyroid state while the respiratory rate remains the same. However, it has long been known (Peabody [12]) that vital capacity is reduced in hyperthyroidism and in like manner the residual air recently has been reported (Robb and Weiss [13]) to be increased in hyperthyroidism and to diminish with improvement in the condition. It is evident, then, that changes in the subdivisions of total pulmonary capacity may depend on functional requirements and need not predicate structural change. Similar changes have been found in patients suffering from congestive heart failure and to this state in these, as well as in patients suffering from hyperthyroidism, the term " functional emphysema " has been applied. This term has been evolved to express the similarity of changes occurring in the subdivisions of total pulmonary capacity in cases of emphysema on the one hand and hyperthyroidism and congestive failure on the other. An effort has been made to carry the similarity further and to describe changes in alveolar blood volume which would reduce the elasticity of, and stiffen, the pulmonary tissue and in this and other ways reduce pulmonary efficiency in a manner similar to emphysema. In the hyperthyroid patient, however, we know that the lung is adequately supplying an increased body oxygen requirement. Is it not reasonable to suppose that an augmented residual air which is properly ventilated by increased tidal air offers a simple way of meeting an increased oxygen demand? That these patients are dyspneic on exertion may be explained by the elevated resting point which in turn necessitates overextension of the chest early in the process of overventilating, but this tendency to dyspnea does not indicate that the respiratory apparatus is not functioning unusually well while the patient is at rest. Seen in this light the condition hitherto alluded to as " functional emphysema " might now be considered as a normal response to an increased demand for oxygen. It seems fair to inquire whether certain changes noted in emphysema patients also may not depend on functional requirements rather than changes in the lung parenchyma.

Conclusions

1. Rebreathing air containing a gradually diminishing oxygen percentage has not been shown to serve as a test for respiratory functional disability in patients thought to have clinical evidence of emphysema.

2. Basal metabolic rate determinations in patients with emphysema seem to yield reliable results.

3. It is important to realize that increase in residual air may constitute one factor in a method of increasing oxygenation of the blood and should not be accepted per se as evidence of reduced pulmonary efficiency.

4. The term "functional emphysema" should not be used since it implies knowledge of emphysema not yet available and may lead to false hypotheses.

5. Reëducation in breathing offers symptomatic improvement to patients suffering from emphysema.

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CLINICAL STUDIES ON VERODIGEN, A DIGITALIS GLUCOSIDE *

By J. P. Baker, Jr., M.D., and Nathan Bloom, M.D., *Richmond, Virginia*

Verodigen, a gitalin-like fraction of digitalis, has been used for a number of years in several European countries, and in some instances has largely replaced the galenical preparations of digitalis. There have been a number of reports on its usefulness,[1, 2, 3] which give the impression that it is considered superior to digitalis in several ways. From a clinical standpoint, it is said to be absorbed more readily and to exert its effect on the heart more rapidly than digitalis. It is claimed, moreover, that this drug is borne by the gastrointestinal tract better, causing nausea and vomiting less often than digitalis.

In this country, Verodigen has been used but a few years. Stroud et al.[4] conducted both pharmacological and clinical studies, finding the qualitative effects of Verodigen to be the same as those of digitalis leaf. By biological assays they found the drug to be 130 times as potent as digitalis; and clinically, to be 360 times as strong—i.e., 1/240 gr. of Verodigen was found to be equivalent to 1.5 gr. of digitalis leaf. These investigators were able to secure complete digitalization with from 1/10 to 1/16 gr., given over a period of five to six days.

In our study, we have used Verodigen on unselected cases of congestive heart failure, both those showing a normal sinus rhythm and those with auricular fibrillation. The group of cases studied in the hospital were kept in bed at conditions as nearly uniform as possible until compensation was restored. In the great majority of cases, no other drugs than occasional sedatives and opiates were used. The ambulatory cases were examined at the out-patient department about once every week. None of these cases had received other digitalis preparations for at least a month before the beginning of Verodigen.

Brief histories of the cases studied in the hospital follow. Table 1 gives the essential features in these cases on admission to the hospital (top line) and after the maximum therapeutic effects had been obtained with Verodigen (bottom line). In those cases showing auricular fibrillation the apical and radial rates are separated by colons.

Abstract of Hospital Cases

D. T., a 41 year old colored male, on admission to the hospital (4/22/35) complained of shortness of breath on exertion for two or three months and swelling of

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TABLE I

Case	Age Years	Sex	Etiologic Classification	Congestive Failure	Weight	Blood Pressure	Pulse	Vital Capacity	Total Verodigen Necessary for Digitalization; Days Administered
D. T.	41	M.	Arteriosclerosis	++++	243	170/120	98	1600	11/80
				0	203	140/75	70	3200	4
G. J.	47	M.	Arteriosclerosis	++	122	170/115	128	1600	6/80
				0	121	130/88	76	3300	3
W. G.	36	M.	Syphilis	+++	149	160/60	102	?	6/80
				0	143	160/56	76	1800	2
H. L.	49	M.	Unknown	+++	—	125/105	100	1100	8/80
				0	—	120/80	84	2600	3
E. W.	52	F.	Arteriosclerosis	++++	190	160/110	120	1100	14/80*
				0	—	130/85	70	2300	6
J. M.	52	M.	Arteriosclerosis	+++	148	170/86	126 : 76	?	9/80
				+	126	136/70	76 : 76	2000	5
Jos. M.	43	M.	Arteriosclerosis	++++	170	216/156	114	1250	9/80
				0	142	190/130	72	2700	3
W. M.	60	M.	Arteriosclerosis	++	176	216/130	108	1700	12/80
				0	161	165/100	80	2500	8
R. D.	64	F.	Unknown	+++	130	180/100	100	—	7/80
				0	125	160/92	72	—	2
A. P.	56	F.	Arteriosclerosis	++++	140	170/104	164 : 142	1400	12/80†
				++	—	150/80	104 : 100	1600	5
C. M.	48	M.	Arteriosclerosis	+++	—	180/112	150	—	8/80
				0		170/90	80	—	3
J. H.	54	F.	Rheum. fever	++++	112	168/105	128 : 104	—	8/80
				0	105	140/80	80 : 80	2300	3

* Lost some by vomiting on second day. Developed extrasystoles sixth day.
† Lost some by vomiting on first and second days.

the ankles for two months. He had continued at work until three weeks prior to admission, when he became too dyspneic. During the past week, edema gradually involved the legs, thighs, scrotum and penis. He had some bloody expectoration four days before admission.

Physical examination revealed marked orthopnea and engorgement of the neck veins. The apex of the heart, in the fifth interspace, extended to the anterior axillary line. Heart sounds were distant. A systolic murmur was audible at the apex. Occasional runs of extrasystoles interrupted an otherwise normal rhythm, the rate being 98. Blood pressure: 170 systolic and 130 diastolic. The lungs showed moist râles over both bases with flatness to percussion over the right base. The liver was palpable well below the costal margin, and a fluid wave could be elicited in the abdomen. The sacrum, genitalia and extremities showed marked pitting edema. A seven-foot roentgenogram showed a transverse diameter of the heart of 21.2 cm. and of the thorax of 34.6 cm.

Laboratory studies: slight anemia; urine—albumin, trace, occasional red and white blood cells and hyaline and granular casts; Wassermann 4 plus.

Cardiovascular diagnosis:

A. Arteriosclerosis; hypertension.
B. Cardiac enlargement, myocardial fibrosis.
C. Regular sinus rhythm.
D. Class III.

On the evening of admission, Verodigen was started, and a total of 11/80 gr. was given in the next three days. During this time the pulse gradually fell to 80 (subsequently to 70); the vital capacity increased to 2300 c.c. (three days later to 3200 c.c.); râles in chest, enlarged liver and peripheral edema cleared up entirely; and there was marked diuresis. It is not to be thought that Verodigen was wholly responsible for the weight loss and diuresis, for 1 c.c. of Salyrgan was given on three successive days.

G. J., a 47 year old colored male, was admitted to the hospital 4/13/35 with a history of two spells of breathlessness, 14 and 11 months previously, both of which had been relieved by some medicine prescribed by his family physician. Three weeks prior to admission, breathlessness returned, as well as several mild attacks of nocturnal dyspnea. Orthopnea had been present in the past few weeks. No history of edema. A past history was given of "bad blood" 12 years ago, for which he received 20 injections in the arm.

On physical examination he appeared slightly dyspneic and orthopneic. The neck veins were not distended. The apex beat of the heart was in the fifth interspace at the mid-clavicular line. There was a systolic murmur at the apex and a markedly accentuated, amphoric pulmonic second sound. The rhythm was regular, the pulse 128, blood pressure 170 systolic and 115 diastolic. The lungs showed numerous moist râles over both bases. There was no enlargement of the liver or peripheral edema. A seven-foot roentgenogram of the chest showed the transverse heart shadow to be 14.6 cm., of the chest 27.9 cm.

Laboratory studies: urine and blood essentially negative. Wassermann negative.

Cardiovascular diagnosis:

A. Arteriosclerosis; hypertension.
B. Cardiac enlargement.
C. Regular sinus rhythm.
D. Class II b.

Verodigen administration was begun the day of admission, a total of 6/80 gr. being given in three days. At the end of this time the pulse had dropped to 80, orthopnea and râles had cleared up and other changes taken place as shown in table 1.

He was continued on a daily dose of 1/240 gr. Verodigen until and after discharge on 4/20/35.

W. G., a colored male, 36 years old, was admitted to the hospital 4/17/35, complaining that nine months previously he had begun having a feeling of fullness in the chest and attacks of paroxysmal dyspnea, especially at night. About the same time he began having a troublesome cough, nocturia and some swelling of the feet. Six months ago he took some heart medicine prescribed by his family physician which did not relieve him much, so he has taken none for the past three months. Inquiry into his past history revealed the fact that he took eight injections "for his blood" two years ago, and that he was operated on for an ischio-rectal abscess in 1932.

On physical examination he showed slight engorgement of the neck veins. His heart was enlarged, the apex beat being 14 cm. from the mid-sternal line in the sixth interspace. There was a prolonged diastolic murmur heard over the aortic area and systolic murmur over the apex and aortic area. The rhythm was suggestive of gallop, rate 120. Blood pressure was 160 systolic and 60 diastolic. Moist râles could be heard over the bases of both lungs. The liver edge was palpable and there was moderate pitting edema of the ankles. A seven-foot roentgenogram of the chest showed the transverse heart shadow to measure 19.6 cm., the chest 29.2 cm.

Laboratory studies: urine essentially negative. Blood showed moderate anemia. Wassermann 4 plus.

Cardiovascular diagnosis:

A. Syphilis.
B. Cardiac enlargement; aortic insufficiency.
C. Regular sinus rhythm.
D. Class II a.

He received 5/80 gr. Verodigen the day of admission with a fall in pulse rate to 80, and 1/80 gr. the day after admission, following which his pulse rate dropped to 76 and remained at that level. He was given a maintenance dose of 1/240 gr. daily. Within four days, all signs of congestive failure had cleared up.

H. L., a 49 year old colored man, was admitted to the hospital 4/23/35 with a history of having caught cold and begun to cough three weeks previously. Following this he developed marked breathlessness and orthopnea. He had had nocturia three to four times since onset of present illness. Nine years ago he had both legs amputated above the ankles on account of frost bite.

Physical examination revealed marked orthopnea and slight engorgement of the neck veins. The heart was slightly enlarged, the apex beat being just outside the mid-clavicular line in the fifth interspace. There was a systolic murmur at the apex and an accentuated P_2. The rhythm was normal, rate 100. Blood pressure was 125 systolic and 105 diastolic in both arms. The chest was emphysematous in type, and there were dullness and râles over both bases. The liver edge was palpable four fingers below the costal margin, and there was moderate pitting edema of the abdominal wall and over the sacral region. Both legs had been amputated about the middle of the tibiae. A seven-foot roentgenogram of the chest showed the transverse diameter of the heart to be 18.1 cm., of the chest 30.6 cm.

Laboratory: urine and blood essentially negative. Wassermann 4 plus.

Cardiovascular diagnosis:

A. Unknown.
B. Cardiac enlargement.
C. Regular sinus rhythm.
D. Class III.

On the day following admission he was started on Verodigen and received 8/80 gr. in the space of three days. During this time his pulse rate dropped to 84, and

signs of congestive failure showed considerable clearing; within two more days they had disappeared altogether. He was given a maintenance dose of 1/240 gr. and remained comfortable.

E. W., a 52 year old white woman, was admitted to the hospital 5/14/35 complaining of paroxysms of dyspnea accompanied by cough, which had begun 15 months previously. These symptoms were much worse when lying down. In the past few days she has noticed swelling of the ankles.

Physical examination revealed an obese woman, quite orthopneic, with neck veins markedly engorged. The heart was enlarged beyond the mid-clavicular line, the extent being impossible to judge on account of her obesity. The rhythm was suggestive of a gallop type, rate 120. Blood pressure 160 systolic and 110 diastolic. Asthmatic breathing could be heard over the upper chest, and numerous moist râles over the bases. The liver was palpable and ascites present. There was moderate pitting edema over the ankles. A seven-foot roentgenogram of the chest showed the transverse diameter of the heart to be 19.7 cm., of the chest 27 cm.

Laboratory studies: unimportant.

Cardiovascular diagnosis:

A. Arteriosclerosis; hypertension.
B. Cardiac enlargement; myocardial fibrosis.
C. Regular sinus rhythm.
D. Class III.

The administration of Verodigen was begun the day of admission and a total of 14/80 gr. given in six days. Vomiting on the second day probably excluded 1/80 or 2/80 gr. During this time the heart rate slowed to 70, and practically all signs of congestive failure cleared up. On the sixth day extrasystoles were observed clinically and electrocardiographically, but there were no other signs of over-dosage. The drug was withdrawn for four days, following which the pulse ranged from 80 to 84. She was discharged on a maintenance dosage of 1/240 gr.

J. M., a 52 year old colored man, was admitted to the hospital 7/17/35 with a history of dyspnea on exertion for the past four weeks with progressive swelling of the lower extremities. During this time he suffered with orthopnea and occasional attacks of paroxysmal nocturnal dyspnea. During the past week he has had a non-productive cough and dull aching pain over the heart. No previous history of decompensation.

On physical examination he was seen to be orthopneic, with marked engorgement of the neck veins. The apex beat of the heart was in the sixth interspace at the anterior axillary line. The rhythm was grossly irregular, the apical rate 126, radial 76, blood pressure 170 systolic and 86 diastolic. Peripheral arteries were tortuous and sclerosed. The lungs showed moist râles over both bases. The liver extended down almost to the umbilicus and there was pitting edema as high as the knees. A seven-foot roentgenogram of the chest showed the transverse diameter of the heart to be 23.8 cm., of the chest 32.2 cm.

Laboratory: urine and blood essentially negative. Wassermann 4 plus.

Cardiovascular diagnosis:

A. Arteriosclerosis; hypertension.
B. Cardiac enlargement.
C. Auricular fibrillation, established.
D. Class III.

Verodigen administration was begun the day of admission, 9/80 gr. being given in four days, and 1/240 gr. daily thereafter. There was a progressive improvement in symptoms and physical signs, coincident with a slowing of the ventricular rate and decrease in the pulse deficit. Within eight days all signs of decompensation had disappeared, and he was discharged later on a daily dose of 1/240 gr. Verodigen.

Jos. M., a 43 year old colored man, was admitted to the hospital 8/11/35 complaining of dyspnea on exertion for the past two months. He had to stop work three weeks ago since when his dyspnea has become progressively worse. A productive cough and nocturnal dyspnea have been troublesome features. Recently his feet and ankles have begun to swell.

Physical examination revealed moderate engorgement of the neck veins. The apex beat was 14.5 cm. from the mid-sternal line in the fifth interspace. The rhythm was normal, rate 114. Blood pressure 216 systolic and 156 diastolic. The lungs showed moist râles over the bases and musical râles throughout. The liver was palpated 5 to 6 cm. below the costal margin. There was pitting edema over the sacrum and of the extremities as high as the thighs. A seven-foot roentgenogram showed the transverse diameter of the heart to be 17.3 cm., of the chest 29.1 cm.

Laboratory: urine showed a slight trace of albumin and rare hyaline casts. Blood showed moderate secondary anemia. Wassermann negative.

Cardiovascular diagnosis:

A. Arteriosclerosis: hypertension.
B. Cardiac enlargement.
C. Regular sinus rhythm.
D. Class III.

Verodigen administration was begun the day following admission and a total of 9/80 gr. given in three days, following which 1/240 gr. was given daily. During this time the heart rate slowed to 68 and all signs of congestive failure cleared up. The diuresis and loss of weight in this case were due largely to the use of Salyrgan.

W. M., a 60 year old colored man, was admitted to the hospital 8/9/35. For the past four months he has suffered with dyspnea on exertion, which has grown steadily worse. Three weeks ago his feet and ankles began to swell. For the past two weeks he has had frequent attacks of paroxysmal nocturnal dyspnea.

Physical examination revealed slight engorgement of the neck veins. The apex beat was 16 cm. from the mid-sternal line in the sixth interspace. The rhythm was normal, rate 108. Blood pressure 216 systolic and 100 diastolic. There was marked sclerosis of the peripheral arteries. Musical and sibilant râles could be heard over both lungs, most marked over the bases. The liver was not palpable, but the extremities showed pitting edema as high as the knees. A seven-foot roentgenogram showed the transverse diameter of the heart to be 18 cm., of the chest 27.9 cm.

Laboratory: urine and blood essentially negative. Wassermann negative.

Cardiovascular diagnosis:

A. Arteriosclerosis; hypertension.
B. Cardiac enlargement, myocardial fibrosis.
C. Regular sinus rhythm.
D. Class II b.

The administration of Verodigen was begun the day of admission and a total of 12/80 gr. given over a period of eight days, with a fall in pulse rate to 80 and a simultaneous clearing of the signs of decompensation. In this case diuresis and weight loss can be attributed largely to Verodigen for no diuretics were given.

R. D., a 64 year old colored female, was admitted to the hospital 9/8/35. She gave a history of dyspnea on exertion and occasional mild attacks of paroxysmal dyspnea for one month prior to admission. She had also had a non-productive cough, edema of the right ankle and nocturia. She had a severe attack of paroxysmal dyspnea just before admission, which caused her to seek hospitalization. Past history negative for cardiac symptoms and anti-syphilitic treatment.

Physical examination, after relief of the immediate attack by morphia, revealed orthopnea and moderate engorgement of the neck veins. The apex beat of the heart

was felt in the sixth interspace at the anterior axillary line. A systolic murmur was audible over the apex. Frequent extrasystoles were present. Pulse 110. Blood pressure 220 systolic and 116 diastolic. There were numerous moist râles over the bases of the lungs. The liver was palpable 3 to 4 cm. below the costal margin, and there was slight pitting edema of the ankles. A seven-foot roentgenogram showed the transverse diameter of the heart to measure 17.9 cm., of the thorax 24.6 cm. A large saccular area extended from the ascending aorta, thought to be aneurysm (confirmed later by fluoroscopy).

Laboratory: Blood—moderate anemia; urine—essentially negative. Blood Wassermann and spinal fluid Wassermann negative.

Cardiovascular diagnosis:

A. Unknown.
B. Aneurysm of ascending aorta; cardiac enlargement.
C. Premature ventricular contractions.
D. Class III.

Verodigen administration was begun the day after admission, a total of 7/80 gr. being given in two days, at the end of which time the pulse rate had fallen to 72, and the signs of decompensation had practically disappeared. She was given a daily maintenance dose of 1/240 gr.

A. P., a 56 year old white woman, was admitted to the hospital 4/11/35. Three weeks before, just after going to bed, she had an attack of wheezing and suffocation which forced her to stand erect for some time in order to get her breath. This was accompanied by very rapid heart action. Following this attack she noticed dyspnea and fatigue when attempting to perform her usual duties, but continued working for one week. During this time her feet became markedly swollen. For the two weeks preceding admission she was unable to do anything, and had to sit propped up most of the time. Her past history was negative except for a "nervous breakdown" three years previously.

On examination it was noted that she was markedly orthopneic and that her neck veins were moderately distended. The apex beat was at the anterior axillary line in the sixth interspace. Rhythm was grossly irregular, apical rate 164, radial 142. The blood pressure 170 systolic and 104 diastolic. There was flatness on percussion over the right lung base, and moist râles on both sides; also râles at left apex. The liver was palpable 3 to 4 cm. below the costal margin. There was moderate edema of the lower extremities.

Laboratory: Urine and blood essentially negative. Wassermann 4 plus.

Cardiovascular diagnosis:

A. Arteriosclerosis, hypertension.
B. Cardiac enlargement; myocardial fibrosis.
C. Auricular fibrillation, established.
D. Class III.

The administration of Verodigen was begun on the day following admission and a total of 12/80 gr. given in five days. The patient vomited several times and some of this drug must have been lost. Of this total 3/80 gr. was given by rectum. At the end of this time, her apical rate was 104, radial 100, she was much more comfortable and showed signs of diminution in her congestive failure. At this time, however, she developed a thrombosis of the right femoral artery, which was removed successfully at operation. Two days later, however, she suffered a fatal hemorrhage from this region.

C. M., a 48 year old white man, was admitted to the hospital 5/29/35, having had marked dyspnea and orthopnea for the past week. During this time he also had a troublesome cough. Six months previously he had an illness with swelling of the

abdomen, which his family physician said was an "enlarged liver due to heart disease."

On physical examination, orthopnea was present, but the neck veins were not distended. The apex beat was 3 cm. lateral to the mid-clavicular line in the fifth interspace. Rhythm was normal, rate 150. Blood pressure 180 systolic and 112 diastolic. Moist râles were heard over both lung bases. The liver edge was palpable 4 cm. below the costal margin, but there was no peripheral edema. A seven-foot roentgenogram showed the transverse diameter of the heart to be 17.4 cm., of the chest 31.7 cm.

Laboratory: Urine—heavy trace of albumin, occasional granular casts. Blood morphology normal. Wassermann negative.

Cardiovascular diagnosis:

A. Arteriosclerosis, hypertension.
B. Cardiac enlargement.
C. Regular sinus rhythm.
D. Class II b.

The administration of Verodigen was begun the day of admission, and a total of 8/80 gr. given in the next three days. During this time the signs of congestive failure cleared rapidly and he was continued on 1/240 gr. daily.

J. H., a 54 year old white female, was admitted to the hospital 9/28/35. Her present illness began about three months previously, with shortness of breath on exertion. Since that time, she had had symptoms of progressive congestive failure, i.e., dyspnea, orthopnea, attacks of paroxysmal nocturnal dyspnea, edema of lower extremities and swelling of abdomen. She was confined to bed for 10 days. Her past history reveals that she had several attacks of rheumatic fever between the ages of 11 and 20 years. She had had several attacks of congestive failure, all of which had been controlled by digitalis.

On physical examination, she showed marked orthopnea and distention of the neck veins. The apex beat was palpable in the fifth interspace 14 cm. from the mid-sternal line. There was a diastolic murmur heard best at the apex, followed by a snapping first sound. A loud systolic murmur was also present. The rhythm was grossly irregular, the apical rate being 128, the radial 104. Blood pressure 168 systolic and 105 diastolic. Moist râles were audible over both lower lungs. The liver was enlarged 3 to 4 cm. below the costal margin and was quite tender. No evidence of ascites was present. There was pitting edema over the sacral region and the entire lower extremities.

A seven-foot roentgenogram of the chest showed the transverse diameter of the heart to measure 16 cm., of the chest, 26.6 cm.

Laboratory: Urine—albumin trace, occasional granular casts. Blood: slight secondary anemia. Wassermann negative.

Cardiovascular diagnosis:

A. Rheumatic fever.
B. Cardiac enlargement, mitral stenosis and insufficiency.
C. Auricular fibrillation, established.
D. Class III.

Verodigen was begun the day of admission, a total of 8/80 gr. being given in three days, at the end of which time all signs of congestive failure had disappeared, and the heart rate had slowed to 80 with no pulse deficit.

Ambulatory patients were followed in the out-patient department of the Medical College of Virginia. None of these cases had been taking digitalis for at least one month prior to starting Verodigen. All of them

SUMMARY OF AMBULATORY PATIENTS FOLLOWED WITH VERODIGEN THERAPY

Case	Age	Sex	Etiologic Classification	Congestive Failure	Blood Pressure	Pulse Rate		Amount Necessary for Digitalization	Maintenance Dose	Period of Observation
						Before	After			
W. B....	60	M.	Arteriosclerosis	+++	170/80?	100?	80	6/80 gr.	1/240 gr.	3 months
J. S.....	56	M.	Arteriosclerosis	++++	180/120?	130?	90	10/80 gr.	1/240 gr.	1 month
C. G.....	77	M.	Arteriosclerosis	++++	180/110	110	70	5/80 gr.	1/240 gr.	2 months*
G. J.....	47	M.	Unknown	+	160/110	90	84	6/80 gr.	1/240 gr.	5 months
W. G....	45	M.	Syphilis	++	150/40	90	90	6/80 gr.	1/240 gr.	1 month*
W. C....	59	M.	Arteriosclerosis	++++	200/120	110	90	5/80 gr.	1/240 gr.	2 months*
R. T.....	46	F.	Arteriosclerosis	++++	180/120	120	85	8/80 gr.	1/240 gr.	1 month
E. B.....	30	F.	Rheum. fever	++	170/110?	120?	90	5/80 gr.	1/240 gr.	1 month
F. M....	48	M.	Arteriosclerosis	++	210/100	105	80	10/80 gr.	1/240 gr.	2 months
H. M....	40	M.	Arteriosclerosis	+++	180/120	110	90	8/80 gr.	1/240 gr.	1 month

* These patients succumbed during treatment.

had some degree of congestive heart failure. Three patients had fibrillating auricles, the others having regular sinus rhythm. Verodigen was administered orally in either 1/80 or 1/240 grain tablets. Each patient was examined at least once every week.

Initial response to Verodigen was excellent, but frequently after the patients began improving, their apparent well being and alleviation of symptoms caused them to discontinue the routine instructions resulting in a return of congestive failure phenomenon. It may be stated unequivocally that after amounts of Verodigen ranging from 8/80 to 10/80 grains, clinical improvement equalling that obtained with digitalis was noted.

Abstract of Ambulatory Cases

W. B., a white male, aged 60, entered the out-patient department on August 20, 1935 complaining of shortness of breath and swelling of his ankles for the past three months. Physical examination revealed a dyspneic, aged white male with engorgement of his neck veins. The left border of the heart was 2 cm. beyond the left nipple line. The rhythm was totally irregular, apical rate 100. Radial rate 80. Blood pressure 170 systolic and 80 diastolic. Moist râles were present in the bases of both lungs. The liver edge was felt 2 cm. below the right costal margin. There was moderate peripheral edema.

Verodigen was given in dosage of 1/80 grain every four hours for six doses, followed by 1/240 grains every night. At the end of seven days, the patient showed remarkable clinical improvement. The venous engorgement had subsided; the moisture in the lung bases was negligible; the heart rate was 84; the radial rate was 80; blood pressure 150 systolic and 70 diastolic; the liver edge could just be palpated; and the peripheral edema had lessened. Three months later, the patient appeared fully compensated taking a daily maintenance dose of Verodigen of 1/240 grain.

Cardiovascular diagnosis:

A. Arteriosclerosis; hypertension.
B. Cardiac enlargement; myocardial fibrosis.
C. Auricular fibrillation, established.
D. Class II b.

J. L. S., a colored male, aged 56, entered the out-patient department on September 3, 1935 complaining of shortness of breath, swelling of his ankles, and nocturia over a period of several months.

Physical examination revealed a dyspneic, moderately edematous, colored male with generalized arteriosclerosis. His neck veins were distended. The heart was moderately enlarged, the rhythm was totally irregular, apical rate 130, radial rate 110, blood pressure 180 systolic and 120 diastolic. There was moisture in both lung bases. The liver edge was palpable at the level of the umbilicus. There was moderate pitting peripheral edema.

Verodigen was given in dosage of 1/80 grain every four hours for 10 doses followed by 1/240 grain every night. At the end of 14 days, the patient was improved. The congestive failure phenomena had lessened; the apical rate was 90; the radial rate was 86; a few moist râles were present in the lung bases; there was moderate peripheral edema. One month later the only sign of decompensation was moderate enlargement of the liver and some edema about the ankles. The radial and apical rate remained about 90.

Cardiovascular diagnosis:

A. Arteriosclerosis; hypertension.
B. Cardiac enlargement.
C. Auricular fibrillation, established.
D. Class II.

C. G., a colored male, aged 77, entered the out-patient department on April 25, 1935 complaining of weakness, shortness of breath on exertion, swelling of his ankles, and frequency of urination, over a period of 12 months.

Physical examination revealed a dyspneic, old colored male with marked generalized arteriosclerosis. The neck veins were distended. The left border of the heart was in the sixth intercostal space, anterior axillary line. The rhythm was regular. The rate was 110 per minute. There were no murmurs. Blood pressure 185 systolic and 110 diastolic. Moist râles were present in both lung bases. The abdominal wall was edematous. The liver edge was palpated at the level of the umbilicus. There was marked peripheral pitting edema.

Verodigen was given in dosage of 1/80 grain every four hours for five doses followed by 1/240 grain every night. At the end of seven days, the patient was less short of breath; the apical rate was 70 and regular. There was still present some moisture in the lung bases and peripheral edema. Two months later, the patient appeared definitely improved except for continuance of the edema, apical rate 70. No arrhythmia. The patient was not seen afterward but communication with his relatives revealed that he had died of some type of lung infection five months after his first visit.

Cardiovascular diagnosis:

A. Arteriosclerosis, hypertension.
B. Cardiac enlargement; myocardial fibrosis.
C. Regular sinus rhythm.
D. Class II b.

G. J., a colored male, aged 47, entered the out-patient department on April 23, 1935 complaining of a sudden attack of shortness of breath that started 24 hours before admission.

Physical examination revealed a very dyspneic colored male, with moderate distention of his neck veins. The chest was full of coarse, bubbling, moist râles. The left border of the heart was 2 cm. beyond the left nipple line in the fifth intercostal space. The rhythm was regular, rate 90, blood pressure 160 systolic and 100 diastolic. There was no definite liver enlargement or peripheral edema.

Verodigen was given in dosage of 1/80 grain every four hours for six doses followed by 1/240 grain every night. At the end of seven days, the patient was clinically improved. The distention of his neck veins and moisture in his chest had disappeared. The heart rate was 84 and regular. He was followed for five months and at no time had any recurrence of dyspnea.

Cardiovascular diagnosis:

A. Unknown.
B. Cardiac enlargement.
C. Regular sinus rhythm.
D. Class II b.

W. G., a colored male, aged 45, entered the out-patient department on April 25, 1935 complaining of shortness of breath and intermittent swelling of his feet and ankles gradually becoming worse in the past nine months.

Physical examination revealed a dyspneic colored male with moderate distention of his neck veins. There were moist râles in both lung bases. The left border of the heart was in the sixth intercostal space at the anterior axillary line. A diastolic

murmur was heard to the left of the sternum in the third intercostal space. The rhythm was regular, rate 90. The blood pressure was 150 systolic and 40 diastolic. There was a definite Corrigan pulse and Duroziez murmur over the femoral vessels. The liver edge was palpable three fingers below the right costal margin. There was moderate peripheral pitting edema.

Verodigen was given in dosage of 1/80 grain every four hours for six doses followed by 1/240 grain every night. After 14 days, the patient could sleep flat in bed, the pulse rate was 90, moisture in the lungs had lessened, the liver edge had receded, the edema of the lower extremities was subsiding. He developed a transperineal abscess in the following month, which ruptured, and while in a weakened state, the patient contracted a lung infection and succumbed in June 1935.

Cardiovascular diagnosis:

A. Syphilis.
B. Cardiac enlargement; aortic insufficiency.
C. Regular sinus rhythm.
D. Class II a.

W. C., a colored male, aged 59, entered the out-patient department on April 23, 1935 complaining of shortness of breath and swelling of his feet for the past three weeks.

Physical examination revealed an elderly, anemic, orthopneic colored male with distended neck veins and marked generalized arteriosclerosis. Moist râles were found in both lung bases. The left border of the heart was in the sixth intercostal space at the anterior axillary line. The rhythm was regular, rate 110, blood pressure 200 systolic and 120 diastolic. There was an apical systolic murmur. The liver edge was felt at the level of the umbilicus. The lower extremities were markedly edematous.

Verodigen was given in dosage of 1/80 grain every four hours for five doses followed by 1/240 grain every night. After seven days, the patient was less breathless; the pulse rate was 84; the blood pressure was 160 systolic and 90 diastolic; the liver edge was felt 2 cm. below the right costal margin; the peripheral edema had lessened. The patient continued clinically improved until May 21, 1935, when he began having paroxysmal attacks of nocturnal dyspnea. On July 1, 1935, he developed an attack of acute pulmonary edema and succumbed.

Cardiovascular diagnosis:

A. Arteriosclerosis; hypertension.
B. Cardiac enlargement; myocardial fibrosis.
C. Regular sinus rhythm.
D. Class II b.

R. T., a colored female, aged 46, entered the out-patient department on August 20, 1935 complaining of shortness of breath, paroxysms of coughing, and swelling of the ankles for the past four months.

Physical examination revealed an anemic, dyspneic colored female with distended neck veins and moisture in the lung bases. The left border of the heart was in the sixth intercostal space 3 cm. beyond the nipple line. The rhythm was regular, rate 120, blood pressure 180 systolic and 120 diastolic. The liver edge could be felt 3 cm. below the right costal margin. There was moderate peripheral edema.

Verodigen was given in dosage of 1/80 grain every four hours for eight doses followed by 1/240 grain every night. After seven days, the patient felt better; the pulse rate was 98; the neck veins were not distended; the moisture in the lung bases had lessened; the liver edge could not be felt; blood pressure was 140 systolic and 110 diastolic. One month later, the patient continued to improve. There was no evidence of congestive failure; blood pressure 150 systolic and 100 diastolic; rate 88.

Cardiovascular diagnosis:

A. Arteriosclerosis; hypertension.
B. Cardiac enlargement.
C. Regular sinus rhythm.
D. Class II b.

E. B., a white female, aged 30, entered the out-patient department on May 16, 1935 complaining of shortness of breath associated with swelling of the ankles for the past two years.

Physical examination revealed a moderately dyspneic, white female. There was no distention of the neck veins. A few moist râles were heard in both lung bases. The left border of the heart was in the fifth intercostal space just beyond the nipple line. The rhythm was totally irregular, apical rate 120, radial rate 100, blood pressure 170 systolic and 110 diastolic. A diastolic rumble was heard over the mitral area ending in an accentuated first sound. The pulmonic second was accentuated. There was moderate peripheral edema.

Verodigen was given in dosage of 1/80 grain every four hours for five doses followed by 1/240 grain every night. After three weeks, breathlessness had lessened; the apical rate was 104; radial rate 100; blood pressure 160 systolic and 110 diastolic; the pulse was still irregular. The patient left the city after her last visit and has not returned to the clinic.

Cardiovascular diagnosis:

A. Rheumatic fever.
B. Cardiac enlargement; mitral stenosis.
C. Auricular fibrillation.
D. Class II a.

F. M., a white male, aged 48, entered the out-patient department on July 26, 1935 complaining of shortness of breath on exertion and swelling of his ankles for the past three weeks.

Physical examination revealed a well developed white male with no distention of his neck veins. A few moist râles were heard in both lung bases. The left border of the heart was in the fifth intercostal space just beyond the nipple line, rhythm was regular, rate 105, blood pressure 210 systolic and 100 diastolic. The liver edge was not palpable. There was moderate peripheral edema.

Verodigen was given in dosage of 1/80 grain every four hours for ten doses followed by 1/240 grain every night. At the end of 14 days, the patient felt better; the pulse rate was 90; there was no evidence of congestive failure. He has continued feeling well and after two months the blood pressure was 190 systolic and 100 diastolic; the pulse rate 80.

Cardiovascular diagnosis:

A. Arteriosclerosis; hypertension.
B. Cardiac enlargement.
C. Regular sinus rhythm.
D. Class II a.

H. M., a colored male, aged 40, entered the out-patient department on July 30, 1935 complaining of shortness of breath, cough, and swelling of his ankles for the past three months.

Physical examination revealed a dyspneic colored male with distended neck veins and moisture in the lung bases. The left border of the heart was in the fifth intercostal space 4 cm. beyond the nipple line. The rhythm was regular, rate 110, blood pressure 180 systolic and 120 diastolic. The liver edge was palpated 3 cm. below the right costal margin. There was moderate peripheral edema. The peripheral vessels were markedly sclerosed.

Verodigen was given in dosage of 1/80 grain every four hours for eight doses followed by 1/240 grain every night. After 14 days, the blood pressure was 170 systolic and 100 diastolic; the pulse rate was 90; all of the congestive failure phenomena were subsiding. One month later, the only evidence of cardiac failure was a few moist râles in the lung bases, pulse rate 90.

Cardiovascular diagnosis:

A. Arteriosclerosis; hypertension.
B. Cardiac enlargement.
C. Regular sinus rhythm.
D. Class II b.

Discussion

The cases in this series were unselected, except that they all showed organic heart disease with congestive failure, and rapid heart rates. None had received digitalis preparations for at least one month previously. Some of them showed auricular fibrillation, others a normal sinus rhythm. The etiology of the heart lesions was in most cases arteriosclerosis with hypertension, in some, syphilis and rheumatic fever, and in others, unknown. In brief, they represent the routine admissions of " congestive heart failure," cases which would ordinarily be treated with digitalis.

It was obvious quite early in our study that the cat unit established experimentally was not an accurate index of clinical dosage. In other words, the dosage determined by biological methods could not be transferred to patients according to the Eggleston method for digitalization. Over and over again, the maximum therapeutic effects were obtained with a dosage far less than that calculated on a basis of the cat unit being 1/80 gr. As nearly as we could judge from a study of our cases, these effects were obtained with approximately 1/3 to 1/2 the calculated dosage. We do not have an entirely satisfactory explanation for this finding. We had expected by analogy with digitalis, that dosages established by biological assay could be used as the basis for human dosage, but we could not confirm this with Verodigen.

It has been contended that the action of Verodigen persists somewhat longer than that of digitalis, an argument which would explain in part the paucity of the required dosage. Since a number of our cases which were followed for several months continued to take only 1/240 gr. of the drug daily, showing neither toxic effects nor return of congestive failure, such a conclusion seems justified. To be able to maintain digitalization with such a small dose (about 1/30 the amount required for digitalization) strongly suggests that the drug is eliminated less rapidly than digitalis. Certainly this was true in the case of biological assays, as shown by Dr. Haag [5] in his experimental studies.

We found that the total amount of Verodigen necessary for complete digitalization varied from 6/80 to 10/80 gr. Those patients requiring the larger doses as a general rule weighed more and required a longer period of time for digitalization. These figures approximate those determined by

Stroud et al. From such findings, we accepted arbitrarily 1/240 gr. as a daily maintenance dose. It was impossible for us to accurately "titrate" human beings, with a class of patients who could remain in the hospital but a limited time. The problem was rendered more difficult by having as criteria symptoms and signs that do not lend themselves to exact measurement. Suffice it to say that those of the group who have been followed over a period of months on such a dosage, showed no evidence of toxic reactions or return of decompensation.

As was mentioned before, the cases in this group were similar to those in whom we would ordinarily have used digitalis. It seems justifiable to say, as a general statement, that the effects produced by Verodigen are qualitatively similar in every respect to those obtained with digitalis. When we analyze the various subjective and objective results in these patients, the truth of such a statement is evident. All of our cases were in congestive failure, the result of heart disease. All showed both subjective and objective evidence of cardiac decompensation. Subjective improvement was shown by the disappearance of dyspnea, orthopnea and other distressing symptoms which ordinarily accompany congestive failure. An analysis of the objective measurements revealed the same improvement; specifically, a slowing of heart rate, together with a decrease in pulse deficit in those patients having auricular fibrillation; an increase in vital lung capacity; disappearance of râles, ascites and edema; diminution in the size in the liver; and finally, an increased output of urine. It may well be argued that some of these results would have been obtained simply by rest in bed. It must be remembered, however, that the majority of these patients had been confined to bed at home without improvement, and further, that drugs of the digitalis group have been shown to be necessary in such cases.

When we come to compare the effects of the drug quantitatively with those of digitalis, there are certain apparent differences. It has been stated by some clinicians that Verodigen produces a therapeutic digitalis action more rapidly than other digitalis preparations. It is true that some of our cases showed excellent therapeutic effects as early as the second or third day, but others required a longer time for complete digitalization. It does seem probable that Verodigen is rapidly and completely absorbed, when we consider the small dose actually required as compared with the dose calculated from biological assay.

Regarding the toxic effects of Verodigen, we have had little experience, for seldom was it necessary to force the drug to such a point. However, we have gained the impression that it is very well borne by the gastrointestinal tract, for it produced no gastric symptoms even in those cases where it was given in overdosages. For example, two of our cases developed extrasystoles after taking large doses of the drug, but showed no loss of appetite or nausea. Another patient, who is not included in this group because his condition was found on further study to be primarily

nephritic, received 1/4 gr. Verodigen before developing nausea, even though he did not vomit and continued to have a good appetite. About the time that nausea appeared, he developed a partial heart block. We had given him this large amount of the drug because he was one of the first cases we studied, and we expected that such an amount would be necessary for digitalization. Another patient, a woman weighing 130 lbs., whom we studied early in our series and who was proved later to have malignant nephrosclerosis, received 1/4 gr. over a period of 12 days, only becoming nauseated toward the end, but not vomiting. About the time that nausea appeared, she developed a coupled rhythm. We mention these two cases to support the contention that large amounts of Verodigen may be taken without producing severe gastrointestinal symptoms. It will be noted from a study of our case records that two of our patients did show vomiting. This was early in the course of administration, however, and ceased even though the drug was continued in the same dosages.

Practically all of these cases had seven-foot roentgenograms made of the chest on admission to the hospital. This was repeated in about half of the cases after we felt that full digitalization had been secured. Invariably the transverse diameter of the heart showed a decrease of 1 to 4 cm. in relation to the diameter of the chest wall.

Electrocardiograms were made on all cases on admission to the hospital, and several times thereafter. We were unable to demonstrate any constant change in the T-wave or S–T interval following Verodigen, except in one case (mentioned above, but not reported in this series) who received 1/4 gr. of the drug over a period of 12 days, toward the end of which time he showed a prolongation of the P–R interval, depression of the T-wave, and finally a partial block. We were not surprised at the absence of electrocardiographic changes, for they have been observed infrequently in our experience during the routine use of digitalis.

Conclusions

From our clinical studies it appears that Verodigen exerts the same qualitative therapeutic effects as digitalis, and provokes the same symptoms when given in overdoses.

Our observations are in conformity with previous reports [4, 6] which definitely indicate that the " biological unit " of digitalis is not always an accurate criterion of clinical dosage. The absorption, potency, and rate of elimination are of equal importance.

In the case of Verodigen the relation of " therapeutic unit " to " biological unit " would seem to indicate a persistence of action which is necessary for a prolonged and uniform digitalis effect.

From our studies so far, we have gained the impression that it is very well tolerated by the gastrointestinal tract, and does not produce gastric disturbances even when administered in moderate overdosage.

Following the oral administration of Verodigen excellent therapeutic effects were noted in many cases as early as the second or third day, although others required a longer time for digitalization.

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A COMPARISON OF THE SYMPTOMS, PHYSICAL AND LABORATORY FINDINGS OF MYXEDEMA AND PERNICIOUS ANEMIA; WITH A REPORT OF THREE CASES *

By JAMES A. GREENE, M.D., *Iowa City, Iowa*

THE clinical manifestations of myxedema and pernicious anemia are sufficiently alike to account for the fact that the former disease is frequently mistaken for the latter. The similarities and differences of the two diseases, however, have not been emphasized. The purpose of this report is (1) to compare the clinical manifestations of the two diseases, (2) to present two cases of myxedema in which it was difficult to exclude pernicious anemia, and (3) to report another case of pernicious anemia and myxedema. The data were obtained from the records of 100 unselected cases of pernicious anemia and 33 cases of myxedema.

Symptomatology. Both diseases are chronic as a rule, with varying degrees of debility. In fact, the debility may be the only presenting symptom. The occurrence of the usual symptoms referable to the hematopoietic, circulatory, gastro-enteric, and nervous systems in the two diseases is listed in table 1.

TABLE I

Occurrence of symptoms referable to hematopoietic, circulatory, gastro-enteric and nervous systems in pernicious anemia and myxedema.

	Pernicious Anemia			Myxedema		
	Pos.	Neg.	Not Stated	Pos.	Neg.	Not Stated
Pallor or anemia	81	8	11	18	6	9
Sore tongue or rectum	57	19	24	3	11	19
Jaundice	59	34	7	5	3	25
Constipation	62	34	4	22	6	5
Alternating diarrhea and constipation	19	70	11	3	27	3
Dyspnea	65	17	18	22	8	3
Edema	33	59	8	25	5	3
Paresthesia	80	12	8	13	5	15
Awkwardness	15	1	84	9	2	22
Ataxia	45	4	51	18	2	13
Mental changes	18	1	81	18	1	14
Slowed up	1	0	99	16	0	17
Cold sensitivity	6	1	93	27	2	4

Since the histories were obtained by different physicians in the routine manner, the frequency of occurrence of the symptoms is not comparable. The symptomatology of the two diseases may be indistinguishable. Sore

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From the Department of Internal Medicine, State University of Iowa Medical School.

tongue and jaundice, which are common in pernicious anemia, may also occur in myxedema, and intolerance to cold and slowness of muscular and mental activity which are common in the latter disease may be present in the former. Paresthesia, which is considered to be one of the cardinal symptoms of pernicious anemia because of its frequency, occurred in more than one-third of the cases of myxedema.

Physical Findings. The general appearance of the patients may be similar. Pallor is prominent in both diseases. Myxedematous deposits do not occur in pernicious anemia but they may be slight and easily overlooked in patients with myxedema. The brownish pigmentation of the skin in myxedema may suggest an icteric tint but the sclerae are clear. While five of the patients gave a history of jaundice, it was not present at the time of examination. The atrophic tongue found in pernicious anemia was observed in three cases of myxedema.

TABLE II

Occurrence of neurological findings in pernicious anemia and myxedema.

	Pernicious Anemia			Myxedema		
	Normal	Diminished	Not Stated	Normal	Diminished	Not Stated
Reflexes	69	27	4	2	22	9
* A.M.R.	19	6	75	3	17	13
Pallanesthesia	18	76	6	13	8	12
Two point discrimination	25	40	35	10	3	20
Pain	56	6	38	14	2	17
Thermal	44	6	50	12	2	19
Cotton	51	6	43	12	2	19
Position	60	16	24	12	2	19
Ataxia	absent 5	present 14	81	absent 7	present 9	17
Paralysis	absent 5	present 0	95	absent 16	present 1	16

* Alternating motion rate.

It is to be noted from table 2 that the neurological changes common to pernicious anemia may also be observed in myxedema. The eight patients with myxedema who showed partial or complete pallanesthesia were less than 50 years of age, therefore the pallanesthesia which is frequently observed in patients over 55 years of age was not a factor. A decrease or loss of the sensations of two-point discrimination and position is rare in myxedema, while it is common in pernicious anemia. On the other hand, a decrease of the alternating motion rate of the tongue or hands is commonly encountered in myxedema but rarely observed in pernicious anemia. Ataxia may be present in both conditions and varies from slight unsteadiness upon turning quickly to complete abasia. An extreme stagger was observed in two patients with myxedema and in two instances abasia was present.

Laboratory Findings. The anemia of myxedema usually has a color

index below 1.0 but in 12 of the cases studied there was an anemia with a color index of 1.0 or above. The red blood cells did not show the marked variation in size and shape that is seen in pernicious anemia and true macrocytes are rarely, if ever, present.

Achlorhydria is perhaps one of the most constant laboratory findings in Addisonian anemia, yet it occurred in five of 14 cases of myxedema. The blood bilirubin (van den Bergh) is usually elevated in pernicious anemia and this was observed in 5 of 11 cases of myxedema. The basal metabolism usually is of value in differentiation of the two diseases, in that it is normal or slightly elevated in pernicious anemia and low in myxedema. A low basal metabolic rate, however, may occur in pernicious anemia during and following the reticulocyte crisis. Alt [1] reported one case in which it was minus 28 per cent and Baldridge and Barer [2] recorded one instance in which the basal metabolic rate fell to minus 20 per cent.

Cases Difficult to Differentiate. In spite of the fact that the clinical picture of the two diseases may be similar, the differentiation is usually not difficult. The difficulties that arise occasionally are illustrated in the following cases:

Case Reports

Case 1. A white married female, aged 55, entered the Indianapolis City Hospital complaining of weakness and numbness of the legs. She had always enjoyed good health except for nervousness and vague gastrointestinal symptoms, until four years before the first admission to the hospital at which time weakness and paresthesias were noted. The symptoms decreased two years later following a blood transfusion but the weakness returned, the paresthesia extended to the hips, and vomiting, diarrhea and slight jaundice were also present at the time of the first admission. There was impairment of pressure, thermal, tactile and pain sensations over the legs. The red blood count was 1,880,000; hemoglobin 38 per cent; white blood count 11,900; and the blood smear showed marked anisocytosis and an occasional nucleated erythrocyte. Marked clinical improvement followed two blood transfusions, but during the next seven years, until readmission to the hospital the following symptoms were noted: A gain in body weight, dryness of the skin, loss of hair, absence of sweating, intolerance to cold, swelling of the hands and feet, decreased mental activity, loss of memory, ataxia and a marked staggering gait. The weakness and paresthesia became increased during the last three years of this period and she was referred to the hospital with a diagnosis of pernicious anemia, but upon examination she was found to have myxedema. The reflexes were sluggish and the lower legs were markedly hyperaphic. Pallanesthesia was present to the twelfth dorsal vertebra and the position and thermal senses were decreased over the legs. A marked stagger was present and the Romberg test was positive. The red blood count was 4,270,000, hemoglobin 86 per cent, and the blood smear was normal. Achlorhydria was present, even after histamine. The basal metabolic rate was 33 per cent below normal.

The myxedema subsided following the administration of desiccated thyroid and the neurological condition improved. Five months later the pallanesthesia and Romberg test were unchanged but marked improvement was noted in the gait and paresthesia.

Case 2. A white married female, aged 57, entered the University Hospital complaining of weakness, inability to walk, and pain in the legs. The patient was well until eight years before admission when she noted ataxia, paresthesia, sore tongue

and pallor. The physician consulted at that time made a diagnosis of a "posterior cord lesion." The red blood count was 2,400,000; hemoglobin 50 per cent; and there was no free hydrochloric acid in the gastric juice. The blood Wassermann was 4 plus. She received antisyphilitic treatment with mercury, bismuth and iodides for six months, with some general improvement. Three years later the pallor increased, jaundice developed and the patient suddenly became unable to walk. Within a few minutes she became unconscious and was taken to a hospital where the red blood count was 1,800,000 and hemoglobin 55 per cent. Achlorhydria was again found and prompt improvement followed liver and liver extract therapy. After two months the red blood count was 4,420,000 and hemoglobin 75 per cent, but reticulocyte counts and a basal metabolic rate were not obtained. She continued to improve but the abasia persisted, and dryness of the skin, loss of hair and gain in weight were noted during the three-year period prior to admission. Liver and liver extract were omitted for six months, she gradually became weaker, and was referred to the hospital with the diagnosis of pernicious anemia.

Upon examination she was found to have myxedema and the following neurological findings: A positive Babinski reflex and a decrease of the sensations of position, two-point discrimination and pallanesthesia of the lower legs.

The red blood count was 3,140,000 and hemoglobin 75 per cent. Achlorhydria was present even after histamine. The blood bilirubin was normal and the basal metabolic rate was 48 per cent below normal.

The reticulocyte count, red blood count, and hemoglobin did not change following adequate amounts of liver extract before and after the myxedema had been controlled with desiccated thyroid gland. Nine months later the neurological symptoms and findings were unchanged and the red blood count was 4,600,000 and hemoglobin 68 per cent.

Although 20 months later the neurological symptoms and findings were unchanged, she was able to walk with the assistance of a cane. The erythrocyte count was 4.4 million and hemoglobin 82 per cent. The intrinsic factor was found to be absent from gastric juice when analyzed by the method described by Castle.[3] The negative result in this case may have been due in part to the small amount of gastric juice obtained, which varied from 50 to 150 c.c. daily. The intrinsic factor, however, was present in comparable amounts of gastric juice obtained from another patient with myxedema who had an achlorhydria without an anemia.

It is difficult to exclude pernicious anemia in the two cases. The normal blood count in the first case is against pernicious anemia, yet spontaneous remissions occur. The failure of the second case to respond to adequate liver therapy before and after the myxedema had been controlled is inconsistent with pernicious anemia, yet there was a primary anemia, a history of definite response following liver and liver extract therapy and the intrinsic factor was absent from the gastric secretions. Cases of co-existing pernicious anemia and myxedema reported by Sturgis and Isaacs [4] and Means, Lerman and Castle [5] had a hematopoietic response following liver extract. However, the anemia of myxedema did not respond to liver extract in the cases studied by Baldridge and Greene [6] and Lerman and Means.[7]

The presence of subacute combined sclerosis in both cases adds to the difficulty, since myxedema is not listed as one of the etiological factors and some neurologists think that it occurs only in pernicious anemia. A review of the neurological conditions that may occur in myxedema by Mussio-Fournier [8] did not include subacute combined sclerosis. Briggs [9] observed

two cases of anemia with myxedema and evidence of combined systemic disease, and thought that they were not true pernicious anemia. Both cases were not improved with thyroid therapy and terminated fatally. Lisser and Anderson [10] insinuate that the presence of cord lesions is of grave prognosis in myxedema, but both of my patients responded to thyroid in the usual manner.

Myxedema and pernicious anemia were the only possible etiological factors for the subacute combined sclerosis in my first case, while syphilis was a possibility in the second case. But negative blood and spinal fluid Wassermanns and normal spinal fluid cell count and globulin during the time the patient was in the University Hospital and the absence of other evidence of syphilis, are strong evidence against syphilis as the etiological agent. If subacute combined sclerosis does occur in myxedema, it adds further to the difficulty in differentiation of pernicious anemia and myxedema in some patients.

The following case is reported as an instance of the coincidence of both pernicious anemia and myxedema:

Case 3. A white male, aged 44, entered the University Hospital complaining of weakness, pain in the right chest, and anemia. He had always been well until 1926 when weakness and jaundice were noted. He went to a well known clinic in June 1927, and was told he had pernicious anemia. The red blood count was 1,610,000 and hemoglobin 33 per cent. He was given a liver diet and the red blood count increased to 2,910,000 and the hemoglobin to 60 per cent. A mild subacute combined sclerosis was present at that time. The patient continued to take a liver diet and liver extract intermittently and felt fairly well. During the two or three years before admission to the University Hospital paresthesia became increased and the following symptoms appeared: Slight dyspnea upon exertion, difficulty of hearing, slowness of speech, loss of hair, thickness of the tongue, slow mental reaction, poor memory and sensitiveness to cold. Seven weeks before admission he developed pneumonia which was complicated by pleural effusion. Following this the symptoms were aggravated and he noted awkwardness in buttoning his clothes. The patient was sent to the hospital with the diagnosis of pernicious anemia and pleural effusion, but upon examination he was found to have pleural effusion and myxedema. Pallanesthesia and absence of the two-point discrimination were found over the lower legs but the position sense was normal. The red blood count was 4,020,000, hemoglobin 58 per cent, and hematocrit 35.5 per cent. The red blood cells in the smear were deeply stained but polychromasia was absent. The size and shape of the cells did not show the variation anticipated for pernicious anemia. A majority of the polymorphonuclear cells contained several lobes. The blood bilirubin (van den Bergh) was normal and free hydrochloric acid was absent from the stomach. The basal metabolic rate was 44 per cent below normal.

With the slight anemia it was felt that the pernicious anemia was not of consequence in the patient's condition and liver extract and desiccated thyroid were given. Prompt improvement in the patient's condition occurred and the red blood count increased to 4,490,000 after one month.

In the cases of coexistent myxedema and pernicious anemia reported by Means, Lerman and Castle [5] the pernicious anemia antedated the myxedema. This was also true in the case just reported. It must be said that if these

instances of the simultaneous existence of the two conditions are evidence of some relationship between them the nature of this relationship remains entirely obscure.

Summary

Although myxedema and pernicious anemia are as a rule easily differentiated, there may be no distinctive features in the history, physical or laboratory findings. The two diseases are not likely to be confused if myxedema is considered in the differential diagnosis of pernicious anemia. The neurological findings, blood smear, and basal metabolic rate are of the greatest value in the difficult cases. Both diseases may be present and a therapeutic test with liver extract may be necessary to ascertain the presence or absence of pernicious anemia, yet a negative response in the presence of subacute combined sclerosis leaves the diagnosis uncertain.

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CONTROL OF THE TOBACCO HABIT *

By JOHN L. DORSEY, M.D., F.A.C.P., *Baltimore, Maryland*

THE physician is frequently called upon to plan a regimen for the patient under his care where it is more or less apparent that some restriction in the use of tobacco is desirable. The indications for such limitation are not clear-cut because the effects of nicotine as a chronic poison to those who habitually smoke to excess are by no means obvious, and are certainly subject to considerable individual variation. Whether nicotine plays a definite part in various forms of vascular disturbance may be open to some discussion, but it is within the practitioner's routine experience to observe that appetite is reduced by smoking, that the sense of general well-being is sometimes adversely affected, that various lesser disturbances (cough, palpitation, nausea, fetor oris, vague indigestion) are at times associated with excessive use of tobacco. Reference to current medical literature shows that the consequences of the abuse of tobacco are being recognized. In the past three years the ill effects of nicotine have been discussed in connection with such varied subjects as peripheral vascular disease, organic and functional diseases of the stomach, pregnancy, headache, hyperglycemia, rhinitis, hypertension, asthma, cirrhosis of the liver, deafness, amblyopia, ether anesthesia, and others. This in face of an endless barrage of propaganda laid down by the tobacco companies in the form of attractive advertising and irresponsible physiology. Some of our "best people" live in a world where one smokes all day long "for digestion's sake," where certain brands of tobacco fail to "get the wind," and are exclusively used by our various champions, where one's private pH is puffed up or down by change in manufacturer—or so at least, according to the back page of almost any magazine. Even our medical journals now carry cigarette advertisements with a scientific flavor. The whole medical directory receives a carton in its mail and any physician who smokes a pack or two is qualified to render a scientist's opinion on the superior merits of the enclosed brand.

It would seem to be accepted that the ill effects of tobacco, whether taken as smoke or otherwise, are largely associated with the nicotine present in the leaf. That a very appreciable amount of this alkaloid is absorbed by the heavy smoker has been demonstrated. The plants from various parts of the world vary widely in their nicotine content, most of our native tobaccos containing a high percentage of the alkaloid. It is also of interest to note that the smoker who does not inhale will absorb only a third less nicotine than the more orthodox smoker, saliva being a solvent for this alkaloid.

If we accept the fact that the use of tobacco in its various preparations is a form of drug addiction, even though a pleasant one not affecting

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criminal statistics, we can more readily help our patient when he finds that his problem has gotten out of hand. Merely to advise that smoking be discontinued is usually futile. The real addict, the smoker of 20 to 50 cigarettes a day, cannot lay aside the habit of years with an easy nonchalance. He has ahead of him wretched days of withdrawal symptoms which will usually end with surrender to the habit which is more deeply rooted than one cares to admit. The moral catastrophe is very like the alcoholic's. Ingenuity is exercised in discovering reasons to escape from the new resolution. In the end, most say in their desperation that no theoretical harm which tobacco might do is enough to make them endure the wretched state of their person, and a return to the old habit very quickly finds them back at the former level of consumption. Marked limitation in tobacco well below a previously established quantity seems more difficult than complete abstinence. In addition to the nervous symptoms which follow withdrawal, the mechanical aspect of smoking or chewing plays some part. After a man has lit a cigar, cigarette or pipe after every meal for many years he will at first be at a loss what to do with his hands at such times. Likewise the confirmed cigarette smoker wants a cigarette between fingers or lips when under any tension.

The first requisite in the cure is a patient who *wants* to stop the use of tobacco in any form. The reasons may be medical, financial, aesthetic, or otherwise, but the determination to discontinue must be there if we are to get any permanent result with the nicotinist—as is true for all addictions.

In an attempt to find some medicinal preparation which would lessen the deprivation symptoms when tobacco is cut off, trial was made of lobelia, which closely resembles nicotine in its effects upon the nervous system.

Lobelia, or Indian Tobacco, the leaves and tops of *L. inflata*, a common wild flower with a blue blossom, was used for smoking and chewing by the American Indians in place of, or mixed with, tobacco. In 1813 Cutler wrote of the use of lobelia in asthma and other spasmodic respiratory conditions. Since then it has been in varying favor for its local and systemic actions, used chiefly by the Eclectic school. Recently its importance has been as a respiratory stimulant.

Lobelia has been shown to contain five alkaloids, chief of which is lobeline, $C_{22}H_{27}NO_2$. Lobeline exerts almost the same effects as nicotine. There is caused a brief stimulation of the motor centers in the spinal cord and medulla. This stimulation is soon followed by depression, and later paralysis with large doses. The feature of the action of the drug is the stimulation of the motor nerve endings in the involuntary muscles. The symptoms of poisoning resemble those of nicotine: nausea, giddiness, faintness, vomiting, cold sweats. The use of nicotine leads to some tolerance for lobeline.

The usual plan has been to have the patient smoke as is his wont on the first day until the mid-day meal is eaten. All use of tobacco is then

abruptly stopped. The first dose of lobeline sulphate, 0.008 gm. (1/8 gr.), is given by mouth in capsule form immediately after the meal. The drug is then further used in the same dosage as the patient may feel the urge to smoke. It has not been found necessary to use over 18 doses in 24 hours and often three or four have been sufficient. The patient decides when a dose is necessary and for how many days he needs this form of substitution therapy. A week of gradually lessening use of lobeline has been ample in most cases, with a few capsules on hand to meet any sudden recrudescence of the former urge. It seems less distressing to start this treatment on a day of rest rather than when the patient is under the pressure of his usual activities.

After the first several doses of lobeline the desire to smoke grows less and less insistent. The hunger returns in waves which are progressively easier to put off without the use of the Indian Tobacco. For a day or two there may be some nausea, a metallic taste, and an uncertain feeling of malaise, but no more unpleasant symptoms have been encountered. As with tobacco, nausea protects against gross over-dosage. The first subjective improvement noted has been a marked increase in the acuity of the olfactory and gustatory senses. One man who had smoked 40 cigarettes daily for at least 15 years said on his third day of lobeline that he was tasting and smelling things which he had almost forgotten. A disconcerting revelation which this latter sense quickly reveals is that the non-smoker suffers in the near presence of the smoker, having lost his protective adaptation. Appetite shows prompt improvement, sometimes to a marked degree, and this can be taken advantage of at once. Nervous, undernourished young women in particular are sometimes seen to undergo a renaissance when tobacco is put away. Likewise, the tense, active, tired man often improves his state of health markedly by interruption of this habit. The irritation of the smoke in the upper air passages is an effect which leaves behind no regrets at its passing. The nasopharynx seems surprisingly clear when freed of this foreign matter. The chronically coated tongue of the heavy smoker loses its covering. Better " wind " is regularly observed. The most gratifying improvement is the increased endurance and the improved sense of well-being which have been reported by former addicts. A definite hypothyroidism developed in two patients about six weeks after tobacco was stopped. It is of interest to consider whether there was any causal relationship here. Another man who had suffered with cold hands and feet for years during the winter, found himself free of this complaint in his first winter without tobacco. Two men use lobeline to restrain their desire to smoke when they must be for some time in places where this practice is prohibited. A " hard night " is distinctly less " hard " when tobacco is omitted. It must, of course, be recognized that excessive use of tobacco may be a result of nervous irritability as well as its cause. Apparently the results have been the same with either sex.

This general plan has been followed out over a period of eight months with a series of patients who had previously tried stopping gradually or abruptly but had all gone back to the pleasant vice. The results have been encouraging. In the great majority of instances it has been stated that there was no comparison between the uneasiness of stopping without lobeline and when this drug is used as a buffer. Once the acute discomforts are passed, the alternate drug is omitted, and then it is a question for the patient to decide whether he thinks it worth while to "stay stopped." He will frequently regret the passing of his former solace but will not again suffer severe pangs for the want of it.

The lobeline can be expected to reduce the misery of deprivation to within relatively easy limits. It is to dull the acute symptoms of withdrawal that the drug is used. After this stage is passed, it is comparatively easy to abstain from tobacco if there is determination to do so.

STUDIES OF THE NITROGEN AND SULPHUR METABOLISM IN A CASE OF CYSTINURIA *

By G. P. Grabfield, F.A.C.P., and B. Prescott, *Boston, Massachusetts*

Since the introduction of satisfactory methods of studying the sulphur partition, a number of cases of cystinuria have been studied without, however, providing a basis for an adequate explanation of the condition. Excellent reviews [1] of the cases so far studied have been published. The metabolic data are confusing and contradictory.[2, 3]

Our purpose was to study the effects of diets high and low in sulphur on the cystine excretion in a patient with cystinuria. As will be seen this could be accomplished only indirectly. On account of the intimate connection between the nitrogen and sulphur metabolism, it was desirable to devise a diet or rather a set of diets in which the nitrogen intake would be constant while the sulphur intake varied. Such a diet would also eliminate the influence of the specific dynamic action reported by Lewis.[4] He found that cystine excretion varied with the total protein of the diet rather than with its cystine content.

To this end we used gelatin as the chief source of dietary protein in our test diets. Such a diet contains a minimal amount of cystine sulphur and is low in total sulphur content. From a practical point of view if the cystine output can be reduced, calculus formation should be delayed.

Our patient was a married woman, aged 35, who had had her first attack of renal colic in the winter of 1928–29. It was not until December 1933 that she was operated upon at the Massachusetts General Hospital and four calculi were removed from the left renal pelvis. They were analyzed by Dr. Fuller Albright and found to be pure cystine, and we are indebted to him for the opportunity of studying this patient. After removal of the stone, the urinary infection cleared up but cystine crystals continued to be present in her urine. She entered the Peter Bent Brigham Hospital for metabolic study in April 1934. At that time she was symptom-free except for marked hysteria, which is recorded as a usual symptom in a large number of these patients. Indeed this was such a prominent feature that it prevented the blood analysis which we had planned. Usual examinations revealed no deviation from the normal except for the presence of cystine crystals and a positive Millon reaction in the urine suggesting the presence of tyrosine. Her family history presented no evidence of the hereditary factor which has been noted in one-third of the reported cases. We had the opportunity to examine the urines of only two siblings and the patient's son, all of which were negative for cystine. No arthritic tendencies were re-

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ported nor were joint deposits found. This patient, therefore, showed calculus formation and markedly hysterical temperament, but failed to show arthritic tendencies or hereditary factors, these four being the usually described clinical features associated with this anomaly. During her stay in the hospital the quantity of cystine crystals varied greatly, as has been the case with all patients observed.

The procedure was that usually employed in metabolic experiments. The diet was calculated from standard tables and duplicate diets prepared, one eaten by the patient, the other analyzed for nitrogen and sulphur. In order to insure constancy, the same foods were eaten every day with particular care to provide the same cuts of meat and parts of vegetables. Table 6 outlines the basic diet and the test diet in which gelatin was substituted as almost the sole source of protein. Urine was analyzed for the various sulphur fractions [6] and certain nitrogenous elements,[7] stools for total nitrogen and total sulphur.

In our hands the Looney cystine method [8] was entirely unreliable, often giving results for cystine sulphur higher than the organic sulphur (cf. table 5). Similar results with this method were obtained by Lewis and Lough and indeed by Looney, Berglund and Graves themselves. Through the kindness of Professor Lewis,[9] but too late for use throughout this study, we were enabled to use his modification of Lugg's [10] simplification of the highly specific Sullivan reaction. In period 6 of the study (table 5) it was found that the figures of the Looney method and this new method checked very closely indicating that perhaps 50 per cent to 70 per cent of the neutral sulphur in our patient consisted of cystine. During this period (the last) the figures by the Looney method were reasonable in relation to the total organic sulphur, whereas in other periods they were obviously too high. Consequently, our results are based on the figures for neutral sulphur.

TABLE I

Showing the sulphur metabolism during the first experiment. All figures represent 24 hour excretion in milligrams. The percentage of the total sulphur is indicated for the various fractions of the urinary sulphur partition.

Period	Time	Total S	Total SO_4		Inorganic SO_4		Ethereal SO_4		Neutral S		Stool S	S Balance
Number	Days	Mg.	Mg.	%	Mg.	%	Mg.	%	Mg.	%	Mg.	Mg.
I. Control	4	634	520	82	473	75	48	7	109	18	92	+ 1
II. Gelatin	4	434	373	86	337	78	36	8	61	14	35	−42
III. Control	4	486	403	83	310	64	99	19	81	17	150	+ 7

We carried out two experiments on this patient. In the first we substituted gelatin for almost all the protein in her mixed control diet. Recognizing that gelatin is incomplete in other respects than cystine, we added

tyrosine and tryptophane to the gelatin diet in the second experiment. This was especially important in that our patient in all probability had a tyrosinuria also. The feeding of tyrosine in a patient with tyrosinuria and cystinuria might throw some light on the suggested anomaly of the intermediary metabolism said to be concerned in cystinuria.

The first table shows a summary of the details of the sulphur excretion in the first experiment. The so-called organic sulphur fraction of the urine contains the excreted cystine. The normal source of this fraction and its constituents are largely unknown. It behaves much like creatinine in the nitrogen partition and is very constant and unaffected by ordinary fluctuations in food intake. It represents on the average 5 to 10 per cent of the total sulphur excretion at ordinary dietary levels. This patient was on a diet of 58 grams of protein and at this level the organic sulphur should be normally less than 10 per cent of the total urinary sulphur. It may be seen that the organic sulphur fraction was high in all three periods but is diminished both absolutely and relatively when gelatin is the principal source of protein in the diet. Not much change is evident in the other sulphur fractions. There is a noteworthy reduction of the stool sulphur during gelatin feeding. Whether this represents altered digestive processes, as is suggested by the fall in ethereal sulphates, or merely an effort to remain in sulphur balance, is not clear. In table 2 are shown the corresponding details

TABLE II

Showing the nitrogen metabolism corresponding to the sulphur figures recorded in table 1. The period numbers correspond in the two tables. Percentages are of total urinary nitrogen.

	Volume	Total N	Urea N		Am. Ac. N		Creatinine N		Fecal N	N Balance
Period	c.c.	gm.	gm.	%	mg.	%	mg.	%	gm.	gm.
I	786	8.0	5.5	69	130	1.6	283	3.5	1.4	−.1
II	1041	9.8	6.3	64	178	1.8	276	2.8	.5	−.9
III	736	7.5	5.7	76	134	1.8	280	3.7	1.5	−.2

of the nitrogen excretion during the first experiment. This patient is in nitrogen equilibrium except during the gelatin period and in this respect behaves normally.[12, 13] The urinary amino acid nitrogen showed a distinct rise in the gelatin period though the concentration is unchanged, owing to a diuresis which in our experience always accompanies the substitution of gelatin as the sole source of protein.

In the second experiment we added tyrosine (1.5) and tryptophane (1.0) to the gelatin diet. In comparing the output during this period with that on the diet containing gelatin alone, it is evident that the addition of these amino acids to the incomplete gelatin reduces both the negative sulphur balance (table 3) and the negative nitrogen balance (table 4). This reduction

TABLE III

Showing the sulphur metabolism during the second experiment. All figures represent 24 hour excretion in milligrams. The percentage of the total sulphur is indicated for the various fractions of the urinary sulphur partition.

Period	Time	Total S	Total SO_4		Inorganic SO_4		Ethereal SO_4		Neutral S		Stool S	S Balance
Number	Days	Mg.	Mg.	%	Mg.	%	Mg.	%	Mg.	%	Mg.	Mg.
IV. Control.....	3	577	452	78	361	63	92	15	125	22	99	+ 3
V. Gelatin plus Amino Acids	5	393	326	83	290	74	36	9	67	17	38	−14
VI. Control.....	3	651	456	72	391	60	65	12	195	28	71	− 1

in negative nitrogen balance cannot be accounted for by the addition of 270 mg. of amino acid nitrogen alone. At the same time, it will be seen that the amino acid excretion rises higher than in the previous gelatin period indicating that some of the ingested amino acid is excreted unchanged or that the ingestion of amino acids in some other way causes an increase in the amino nitrogen in the urine. This period is the only one in which the

TABLE IV

Showing the nitrogen metabolism corresponding to the sulphur figures recorded in table 3. The period numbers correspond in the two tables. Percentages are of total urinary nitrogen.

Period	Volume	Total N	Urea N		Am. Ac. N		Creatinine N		Fecal N	N Balance
Number	c.c.	gm.	gm.	%	mg.	%	mg.	%	gm.	gm.
IV	862	8.7	5.6	64	122	1.4	290	3.3	1.3	−.3
V	851	9.3	6.2	67	250	2.7	280	3.0	1.1	−.5
VI	803	6.8	4.5	66	159	2.3	280	4.1	1.9	+.5

amino acid excretion is above the usually stated normal. Such figures are 1 to 2 per cent [3] of the total nitrogen or a concentration of less than 20 mg. per 100 c.c.[13] In table 4 it will be seen that the amino acid excretion exceeds 2 per cent of the total nitrogen in the last two periods, but in the last period the concentration is just below 20 mg. per 100 c.c. However, the excretion in the fifth period is increased over the normal by both the criteria mentioned. In period 2, when gelatin alone was fed, the amino acid nitrogen excretion rose from 130 to 178 mg. During period 5 the amino nitrogen excretion was 250 mg. Thus the addition of 270 mg. of amino acid nitrogen to the gelatin diet was followed by an increase of 72 mg. in the urinary excretion. Since the after period showed a somewhat higher figure than before we may add 25 mg. to this figure as total extra amino nitrogen excretion after feeding amino acids. This figure is 20 mg. less than the

tyrosine nitrogen fed and suggests that some of the tyrosine must have been utilized even if all of the tryptophane was. However, we can say with certainty that about three-fifths of the amino acid nitrogen ingested by this

TABLE V

Showing relation between cystine excretion determined by Looney method and related urinary constituents in the two experiments. It will be seen that this method yielded results that were obviously too high in the first experiment though they closely paralleled the neutral sulphur. The periods are numbered to correspond with the other tables.

Period	Neutral S Mg.	Cystine S Mg.	Cystine S / Neutral S %	Amino Ac. N Mg.	Cystine N Mg.	Cystine N / Amino N %
I	109	142	130	130	63	48
II	61	111	182	178	49	28
III	81	125	155	134	56	42
IV	125	102	82	122	48	39
V	67	66	98	250	29	12
VI	195	112	57	159	50	31

patient was deaminized. It is evident, therefore, that this patient with cystinuria and tyrosinuria can utilize only part of ingested amino acids other than cystine. The normal organism excretes all ingested amino acid as urea, and Lichtman [14] has shown that even most patients with hepatic disease can oxidize two grams of tyrosine fed by mouth.

TABLE VI

A tabular view of the diets fed as calculated from standard diet tables. In the other tables the nitrogen and sulphur balance is figured on the results of actual analysis of the food eaten.

	"Normal" gm.	"Test" gm.
Protein	58	58 (45 gelatin)
Carbohydrate	173	132
Fat	125	118
Calories	2049	1831
Water (including that in food)	1809	1838
Sulphur	0.69	0.14
NaCl	1.57	0.75
Added NaCl	2.00	3.00
Total NaCl	3.57	3.75

In both our experiments this increase in amino acid nitrogen excretion was accompanied by a diminution of cystine nitrogen as estimated from the organic sulphur excretion. However, the increased amino acid excretion might conceivably be due to failure of a deamination in the kidney, as

Krebs [15] has shown that isolated renal tissue possesses powerful deaminizing powers and has postulated that ammonia formation observed by Nash and Benedict [16] is a result of this deamination and is regulated by the neutrality needs of the organism. Unfortunately such studies were not carried out on this patient.

These experiments do not support the idea that cystine output is solely dependent upon the specific dynamic action of protein. These studies may be interpreted as in accord with the hypothesis that this anomaly is concerned with the intermediary metabolism.

In view of the diminution of organic sulphur excretion when gelatin is fed, it seems logical to conclude that the liberal use of gelatin in the diets of these patients might be a useful therapeutic procedure.

Summary

1. A case of cystinuria was studied metabolically on high and low sulphur diets using gelatin as a substitute for other protein in the test diet.

2. The cystinuric maintains a normal nitrogen and sulphur balance.

3. Gelatin feeding decreases the cystine output (as measured by the organic sulphur fraction of the urine) both absolutely and relatively.

4. The negative sulphur and nitrogen balance during gelatin feeding is diminished by adding tyrosine and tryptophane to the diet.

5. Evidence is supplied by these experiments to support the hypothesis that this anomaly concerns the intermediary metabolism and that in this case other amino acids are abnormally handled.

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THE USE OF HISTIDINE HYDROCHLORIDE (LAROSTIDIN) IN THE TREATMENT OF PEPTIC ULCER *

By JOHN T. EADS, M.D., *Philadelphia, Pennsylvania*

DURING the past three years a great deal of interest has been aroused by reports of the use of histidine hydrochloride (Larostidin) in the treatment of peptic ulcer. Due for the most part to favorable immediate results reported, this particular substance has enjoyed a widespread usage. In very few of the reports has there been a sufficient follow-period of observation for really accurate estimation of its true worth in comparison with the time honored dietary and alkaline régime. It has been the hope of the users of this treatment that the long drawn-out medical treatment of peptic ulcers could be avoided and that immediate and lasting improvement would follow. The earliest reports on immediate results were optimistic and tended to bear this out, but subsequent reports and two very recent ones have to a certain extent indicated the fallacy of this hope.

This treatment was introduced by Weiss [1] and Aron [3] of Strasbourg in 1933. Experimental ulcers were produced in dogs after the method of Mann and Williamson.[2] These ulcers were considered caused by the lack of duodenal juice and its effect on the digestion of proteins. The investigators treated these ulcers by using various combinations of amino acids and produced favorable healing results in a small series of animals. Weiss and Aron [4] then treated ulcer patients, at first with a combination of histidine and tryptophan, and reported evidence of healing. Later the use of histidine alone was found, by Aron,[5] to produce the most favorable results.

Since this experimental work many other foreign authors have reported their results in the use of injections of histidine hydrochloride in the treatment of peptic ulcers in humans. Among these are Lenormand,[6] Bogendorfer,[7] Hessel,[8] Bulmer,[9] Stolz and Weiss,[10] and Blum.[11] Most of these authors report the immediate results in small series of cases and for the most part these results have been uniformly impressive. They have reported not only prompt symptomatic relief, but disappearance of roentgenographic signs and reduction in gastric acidity.

In only one or two instances has a follow-up period been of sufficient length to determine what happens to the excellent immediate results reported. Weiss,[12] in a late report, reports on the treatment of 91 ulcer patients over a period of 18 months.

In this country there have been fewer reports. Volini and McLaughlin [13] reported on a series of 21 patients in 1935. In 1936 Volini

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From the Medical Department, Jefferson Hospital, Philadelphia. The preparation of Histidine solution used in this series of treatments is Larostidin supplied by Hoffmann-La-Roche, Inc., Nutley, N. J.

and McLaughlin [16] reported on 73 patients, a continuation of their previous preliminary report. They report in both publications 79 per cent of the cases clinically improved after six months with 21 per cent failures. They also report diminution in gastric acidity.

Eads [14] made a preliminary report on the treatment of 35 cases of peptic ulcers with histidine with 65 per cent showing immediate clinical improvement and 35 per cent considered as failures. He found little or no effect on the acid curve. Six of his cases presented roentgenographic evidence of disappearance of the ulcer deformity.

Rafsky [15] reported a series of 26 cases so treated with symptomatic relief obtained in 19 over a four-month period. He observed marked reduction of acid. Practically all of these reports were made on ulcer patients treated as ambulatory cases and with little or no dietary restrictions.

The latest reports on the use of histidine hydrochloride in the treatment of peptic ulcer are those by Sandweiss [17] and Martin.[18] These authors treated a series of 40 patients and 41 patients, respectively. They had also a control series of patients treated with diet and alkalis for approximately the same length of time with follow-up periods of one year or more. They, too, found some very favorable immediate results from the use of histidine treatment but after an observation period of from a few months to a year or more found a high percentage of recurrence of symptoms—higher in those patients treated with histidine than in the series treated with diet and alkalis alone.

Sandweiss reports that 85 per cent of patients showing remissions of symptoms due to the histidine treatment returned with ulcer symptoms within six months after treatment. He does not advise the routine use of histidine in the treatment of peptic ulcers but believes it may have a place as an additional weapon in the regular medical treatment armamentarium.

Martin found that his percentage of recurrences was larger than in those cases treated by diet and alkaline therapy. He felt that the results of histidine therapy were symptomatic and transient.

Both Sandweiss and Martin report very little effect on the gastric acidity in their series of cases treated with histidine hydrochloride.

The present report deals with 85 cases of peptic ulcer which have been treated with daily intramuscular injections of a 4 per cent solution of histidine hydrochloride. The number of injections has varied from 15 to 36 with 70 cases receiving 24 injections each.

Each patient was diagnosed definitely a case of peptic ulcer, clinically and by positive roentgenographic findings.

There were 77 cases of duodenal ulcer and 8 cases of gastric ulcer. The average duration of symptoms was six years. The shortest history of symptoms was two months and the longest history indicated 12 years' duration. Fifty-five of these cases had been on previous ulcer treatment, usually consisting of some form of dietary restriction plus alkaline medication.

Eight of these patients had undergone previous surgical operations for their conditions—two having had a perforated ulcer with repair and six having had gastro-enterostomies.

In the majority of cases several analyses of the gastric acidity were made before, during and at the completion of the course of treatment.

All were examined roentgenologically before institution of the treatment, several during the course of the treatment and all at the completion of the course.

Records were kept with regard to symptomatology, weight, et cetera, during the course of treatment.

Sixty cases were treated as strictly ambulatory cases with little or no dietary restrictions. Twenty-five cases were treated as hospital cases, but not confined to bed. Ten of these were restricted somewhat as to diet and given occasional doses of alkalis.

The patients have been separated into two groups—one group of 45 cases which has been followed for a period of approximately 18 months, the other group of 40 cases which has been followed for a period of six months.

Immediate Results of Histidine Treatment

There were no untoward reactions in any of the cases treated. Temperatures, blood pressures, pulse rates and blood counts were unaffected.

There was very little alteration in the gastric acidity. Only eight patients showed any appreciable diminution in acidity and these were those having marked hyperacidity.

Eight patients presented roentgen-ray evidence of immediate healing by disappearance of radiological signs of the ulcer. About half of the remainder showed some improvement in the roentgen-ray findings, such as lessened irritability, spasticity and tenderness in the region of the ulcer deformity. The remaining patients exhibited no change in the roentgenologic findings. Gastric ulcer patients presented the best response to the treatment from the roentgenologic point of view.

Those patients presenting evidence of obstruction were not benefited by the injections and in two cases were made worse by the treatment.

All of the cases previously operated upon showed immediate signs of improvement clinically. Five of these remained clinically improved after one year of observation.

A gain in weight accompanied clinical improvement. In some instances this was quite rapid. However, while this gain in weight persisted during the active treatment, it tended to drop off and even be lost during the follow-up observation period in many instances. An increase in appetite and sense of well-being was also experienced in those cases showing immediate improvement.

In most cases in which clinical improvement was noted it appeared early in the course of treatment, usually before five injections had been given.

In only a few of the cases which showed improvement, was the suggested full number of 24 injections given before relief was obtained. In six cases, 36 injections were given without benefit. In a few cases after 24 injections had been given, there was some improvement noted a few weeks after completion of the course. This suggested some delayed benefit, but it was not permanent. Generally, those cases showing the greatest clinical improvement did so after only a few injections; those having 24 or more injections showed the poorest response.

Gastric ulcers presented the best response clinically as well as from the roentgenologic point of view. Those patients in the younger group with shorter histories and with no complicating factors such as obstruction or hemorrhage also responded more rapidly and more completely to the treatment.

The following tables show results in the two groups of patients, and the percentage of recurrences in those cases showing immediate improvement. These 85 cases have been observed over periods varying from six to 18 months. There are 10 other cases which have been treated but are not included in this series because they failed to return for check-ups and their records are incomplete.

TABLE I

45 Cases: 39 Duodenal Ulcers, 6 Gastric Ulcers

Observation time	X-ray healed	X-ray improved	Clinically improved	Unimproved	Recurrence of Symptoms
1 month	6	13	28 (62.2%)	17 (37.7%)	—
6 months	6	11	18 (64.3%)	—	10 (35.7%)
12 months	5	9	14 (50%)	—	14 (50%)
18 months	5	4	9 (35.7%)	—	18 (64.3%)

From table 1 can be seen that of the 28 cases showing immediate evidence of healing 35.7 per cent presented recurrence of symptoms within six months. At the end of 18 months 64.3 per cent show a return of symptoms.

TABLE II

40 Cases: 38 Duodenal Ulcers, 2 Gastric Ulcers

Observation time	X-ray healed	X-ray improved	Clinically improved	Unimproved	Recurrence of Symptoms
1 month	2	14	23 (57.5%)	17 (42.5%)	—
6 months	2	6	9 (39.2%)	—	14 (60.8%)

In table 2, 23 cases, or 57.5 per cent showed clinical evidence of healing. Of these, after a six months observation period 14 cases or 60.8 per cent presented a return of their symptoms. This group comprised older patients with longer histories than the group outlined in table 1. There were only

two gastric ulcers in this group both of which presented both roentgen-ray and clinical evidence of healing and remained well. Four of the cases in this group showed evidence of obstruction and did not benefit at all by the treatment.

Discussion

It would seem therefore from the literature on the subject of histidine hydrochloride therapy in the treatment of peptic ulcers that whereas the immediate results secured may be generally favorable, this favorable effect is not continued in a large percentage of cases.

The mechanism by which histidine therapy produces benefit in those cases showing immediate improvement is by no means satisfactorily explained. The theory of Weiss and Aron postulated a deficiency in protein metabolism, with consequent loss of mucosal resistance. It is not accepted by many investigators. Some have held that the stimulation of an increased secretion of mucin might have a bearing, others that there is an analgesic effect produced by the injections. No doubt some of the favorable effects may be due to a psychic effect produced by the injections of a new substance with a considerable reputation. The true mechanism is not yet fully understood.

As other observers have found, the immediate results obtained in the use of histidine hydrochloride are excellent in a large number of cases of uncomplicated peptic ulcer. They compare very favorably with the best results obtained from the rigid dietary, alkaline regimen. However, their end-results after fairly short observation periods are not as good as the end-results following the orthodox medical treatment.

Yet, there seems to be a place for the use of histidine in the treatment of peptic ulcers, for in many cases relief of symptoms is so prompt and so spectacular that this immediate effect alone would justify its use. It would seem logical to employ this new agent as an adjunct to our regular medical treatment.

From the observation of its usage so far reported, histidine hydrochloride therapy cannot supplant the dietary-alkaline medical treatment, but it may be a valuable addition to this treatment, particularly in those cases which do not respond readily to the orthodox measures. In those cases in which further surgery is contraindicated histidine therapy offers aid, such as marginal ulcers and reactivated ulcers following surgical procedure. No attempt has been made to institute a second course of injections after six months in order to determine if there would be any benefit resulting from such a procedure. It might be well to do this.

Conclusions

Follow-up periods of from six months to 18 months have shown that the favorable results obtained immediately during the active course of treatment

with histidine hydrochloride are not continued in from 35 per cent to 65 per cent of the cases.

From the present indications it would appear that the use of histidine alone offers end-results of less lasting benefit than the regular dietary and alkaline therapy in the average peptic ulcer patient. However, combined with the regular orthodox medical treatment, histidine may hasten the good results expected. It certainly is worth trying in those cases resistant to the usual treatment. Further study of the histidine injection treatment should be continued.

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THE RELATIONSHIP OF BACILLARY DYSENTERY TO DISTAL ILEITIS, CHRONIC ULCERATIVE COLITIS AND NON-SPECIFIC INTESTINAL GRANULOMA *

By JOSEPH FELSEN, M.D., *New York, N. Y.*

THE purpose of this communication is to present for critical consideration certain data which have been collected to support the contention that acute bacillary dysentery, acute and chronic distal ileitis, chronic ulcerative colitis and chronic non-specific intestinal granuloma have a common pathogenesis. The evidence to be offered will be considered under the following sub-divisions, viz.: epidemiological, clinical, serological, bacteriological, pathological and roentgenographical. An effort will then be made to correlate the findings reported under the respective headings and to apply them in diagnosis and therapy. The material which forms the basis for this study includes 400 cases of acute bacillary dysentery (1 major epidemic, 6 minor outbreaks, sporadic cases), 29 cases of acute distal ileitis, 22 cases of chronic distal ileitis, 18 cases of combined chronic ileocolitis and 84 cases of chronic ulcerative colitis. The period covered is from September 1933 to June 1936. These data are supplemented by a 9 to 12 months follow-up study of the Jersey City epidemic which has covered 122 out of an original group of 210 hospitalized patients.

EPIDEMIOLOGY

In the United States the seaport cities are the chief endemic areas for acute bacillary dysentery. The general geographic distribution of acute distal ileitis, chronic distal ileitis and chronic ulcerative colitis corresponds to that of bacillary dysentery. Inquiries show that there are no published or unpublished statistical data now available on these diseases from any source, including the United States Army, United States Public Health Service and the American Public Health Association. The reason is obvious, as ileitis, chronic ulcerative colitis and non-specific granuloma have been regarded as diseases of uncertain etiology. The increasing frequency of observation of these diseases during the last decade is believed to be associated with the increase in bacillary dysentery and not due merely to greater keenness in diagnosis. Outbreaks of dysentery in the New York area occur both in winter and summer, often in hospitals through improper isolation of unrecognized cases.

Contact infection in chronic distal ileitis and chronic ulcerative colitis occurs chiefly during the stage of acute bacillary dysentery when the specific

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From the Department of Laboratories and Research, The Bronx Hospital, New York, N. Y.

organisms are present in the feces. The incidence of contact infection in this series of reported cases of chronic disease is 37.4 per cent, a rather high figure since the original source of infection is difficult to determine after one or more years have elapsed. Conjugal infection is relatively common if the couple were married prior to the onset of the original attack of bacillary dysentery or if one partner, involved prior to marriage, still harbors the

FIG. 1. Acute bacillary dysentery (Flexner Y), Stages 1 and 2. Arrow points to hyperplastic lymph nodules (Stage 1). Scattered over the remainder of the mucosa are multiple areas of focal lymphoid necrosis appearing like the mouths of tiny diverticula (Stage 2).

organism. Evidence of conjugal infection occurred in cases 5, 10, 35, 43 (table 1). This does not necessarily signify that both husband and wife will develop chronic ulcerative colitis, or ileitis, but that clinical and laboratory data will often reveal the presence of a previous dysentery infection with the same organism in both.

Because of the importance of epidemiological studies in establishing the pathogenesis of the chronic intestinal lesions a brief summary of some of the

cases will be given. In each instance there was a coincident time factor and the chronic disease represented a definite continuation of the acute phase in a previously healthy individual. Except where otherwise specified the laboratory studies were made in the chronic stage. Titers given refer to the agglutinating power of the patient's serum for dysentery bacilli. In contact cases the titers given are for the same strain of the organism.*

TABLE I

Chronic Ulcerative Colitis—84 Cases

No.	Sex	Age	Duration yrs.	Agglut.	Culture	Phage	Epidemiology	Surg. Path.	Necropsy	Roent.
1	F.	19	1⅙	PH 160			+			+
2	M.	45	15	PH MD 320	0	0	+			+
3	F.	32	½	PH MD 160						+
4	F.	27	2½	PH 320						+
5	F.	32	19	MD PH 160		+	+			+
6	F.	29	2½	MD PH 320	0	0				+
7	M.	50	¾	MD PH 320	0					+
8	F.	41	1	PH 320		+		+		+
9	M.	20	4	MD 160	0	+				+
10	F.	35	3	MD 160		+	+			+
11	F.	41	1	F 100	+F		+			
12	F.	33	4	MD 640	0	0				+
13	M.	31	½	PH 160	0	+				
14	F.	35	14	MD 320						+
15	M.	40	½	PH 320			+			
16	M.	35	½	PH 100	0	0	+			
17	M.	28	3	PH 160	0	0				
18	M.	47	1	MD PH 160	+MD	+				+
19	M.	36	2	PH 100	0					+
20	M.	22	11	SD 40						+
21	M.		1	MD PH 100			+			+
22	M.	22	1	MD 100	0		+			+
23	F.	28	1½	F 160						
24	F.	40	7	PH 640 MD F 320						
25	F.	11	⅙	MD 40	0					
26	F.	41	6	MD 640	0	0				
27	M.	42	½	MD 320						+
28	M.		2½	MD PH 160						+
29	F.	36	16		+SD		+			+
30	F.	27	5	PH 240	0	+				+
31	M.	22	2	PH 320	0					+
32	M.	28	7	F 160						+
33	M.	34	6	SD 50						+
34	F.	35	4	MD 160	0					+
35	M.	37	1½	MD 640	0		+			+
36	M.	35	6	PH 320	0	0	+			+
37	F.	38	½	PH 160	0	0				
38	F.	47	1	0			+			+
39	M.	38	1				+			+
40	M.	22	2	MD 640	+MD	+	+			+
41	M.	27	2½	F 160						+
42	M.	8	2	MD 320						+

* The writer wishes to gratefully acknowledge the many courtesies extended to him by the physicians and institutions it was his privilege to serve and who furnished much of the antecedent and follow-up clinical data.

TABLE I—*Continued*

No.	Sex	Age	Duration yrs.	Agglut.	Culture	Phage	Epidemiology	Surg. Path.	Necropsy	Roent.
43	M.	50	1	PH 100		+	+			
44	M.	29	1	JC 320			+			+
45	M.	53	1	MD 160	0	0			+	+
46	F.	35	1	F MD 160						+
47	M.	24	½	PH 320	0					
48	F.	20	1	MD PH 320	+MD	0				+
49	F.	31	1	S 640	+S		+			
50	M.	16	¼	PH 80						
51	F.	26	½	MD 320	+MD	0	+			+
52	M.	35	6	MD PH 160						
53	M.	36	2	PH 160	0	0				
54	M.	28	3	PH 100	0	+	+			
55	M.	22	1½	F 160		+	+		+	+
56	F.	35	6	F 320	0		+			
57	M.	33	10	PH 640	0					+
58	F.	19	½	MD 320	0					
59	F.	57	19	MD 120	0	+	+			
60	M.	19	⅓	PH 160						
61	M.		1				+			+
62	F.	35	¼	SD 80	0					+
63	M.	13	5	MD 320	0	0	+			+
64	M.	30	6	MD 160	0	0				
65	M.	14	2	MD 160		+				+
66	M.	5	5	MD 160						+
67	M.	26	12	MD 320		+	+			+
68	M.	22	5	MD PH 160	0	0	+			+
69	F.	30	7	PH 320	0					+
70	F.	25	1	MD PH 100			+			+
71	F.	28	3	PH 40	0	+				
72	M.	44	½	MD 640	0	+	+			
73	F.	13	2	MD 160	0	0	+			
74	F.	40	1	F 320			+			+
75	M.	33	7	PH 320						+
76	M.	19	1⅓	PH 100	+PH		+			
77	M.	40	2½	PH 100			+			+
78	M.	35	6	PH 320	0	+	+			
79	F.	16	¾	MD 160	0	0				+
80	F.	28	½	MD 320	0	0				+
81	F.	20	1	SD 160	0					+
82	F.	38	7	PH MD 160	0					+
83	F.	22	5	F 240	0	+				+
84	M.		1	F 240			+			+

Note: In this and the following tables empty spaces indicate no examination made. "0" signifies negative, "+" signifies positive, F (Flexner Y), MD (Mt. Desert), PH (Park-Hiss), SD (Sonne-Duval), S (Schmitz). These strains are all of the mannite-fermenting Flexner type. Owing to the heterogeneity of the Flexner antigen several strains were sometimes agglutinated by the same serum. Only highest titers are given, except where a special point of interest is involved.

EPIDEMIOLOGICAL DATA IN CASES OF CHRONIC ULCERATIVE COLITIS (TABLE 1)

Case 2. Male, aged 45. Duration of disease 15 years. Started during outbreak of dysentery in U. S. Army, A.E.F., during the World's War. Titer 1:320.

Cases 59 and 5. Mother, aged 57 and daughter, aged 32. Original infection contracted in China 19 years ago. Mother's titer 1:120. Daughter's titer 1:160. Bacteriophage present in feces of both. Daughter's husband of a recent marriage (three months) now has ulcerative colitis and shows a titer of 1:160 against the

same strain. Two of her children by a previous marriage have had repeated attacks of bloody diarrhea since birth, diagnosed as "colitis." These children are now being treated for colitis abroad.

Case 10. Female, aged 35. Duration three years. Titer 1:160 and bacteriophage present in feces. Husband had acute dysentery at time of onset of wife's symptoms and now has a titer of 1:100.

Case 11. Female, aged 41. Duration one year. Started during outbreak of acute bacillary dysentery in Mexico City. Three others in party definitely diagnosed by attending physician. Titer 1:160. Fecal culture positive.

Cases 15 and 16. Male, aged 40. Duration one-half year. Titer 1:320. Male, aged 35, brother, duration one-half year, titer 1:100. Child of latter has had diarrhea for approximately one-half year, titer 1:100. Two others in family affected but not examined.

FIG. 2. Acute bacillary dysentery (Mt. Desert), Stage 3. Discrete and confluent ulceration.

Case 21. Male, age unknown. Duration one year. Follow-up of Jersey City dysentery epidemic.[1]

Case 22. Male, aged 22. Duration one year. Titer 1:100. Sister admitted to hospital with appendicular form of acute bacillary dysentery, and at operation there was found acute distal ileitis with mesenteric and mesocolic lymphadenitis. Fecal culture positive and bacteriophage present. Titer 1:100.

Case 35. Male, aged 37. Duration one and one-half years. Titer 1:640. Wife affected during acute stage. Titer 1:160.

Case 38. Female, aged 47. Follow-up of Jersey City epidemic.

Case 39. Male, aged 38. Duration one year. Follow-up of Jersey City epidemic. A son, who was also affected during the epidemic, is free of symptoms.

FIG. 3. Case 55, table 1. Chronic ulcerative colitis with polyposis cystica. Arrow points to ileocecal valve. Accession No. 7160.

FIG. 4. Case 3, table 2. Obstructive granulomatous lesion in distal ileum. Accession No. 7938.

Case 40. Male, aged 22. Duration two years. Titer 1:640. Fecal culture positive and bacteriophage present. At onset of disease nursed friend ill with "dysentery" who afterwards died. The necropsy findings were chronic distal ileitis and chronic ulcerative colitis with polyposis cystica.

Case 43. Male, aged 50. Duration one year. Titer 1:100. Bacteriophage present in feces. Wife had dysentery at onset of patient's disease. Titer 1:160.

Case 44. Male, aged 29. Duration one year. Follow-up of Jersey City epidemic.

Case 49. Female, aged 31. Duration one year. Titer 1:320. Dysentery started

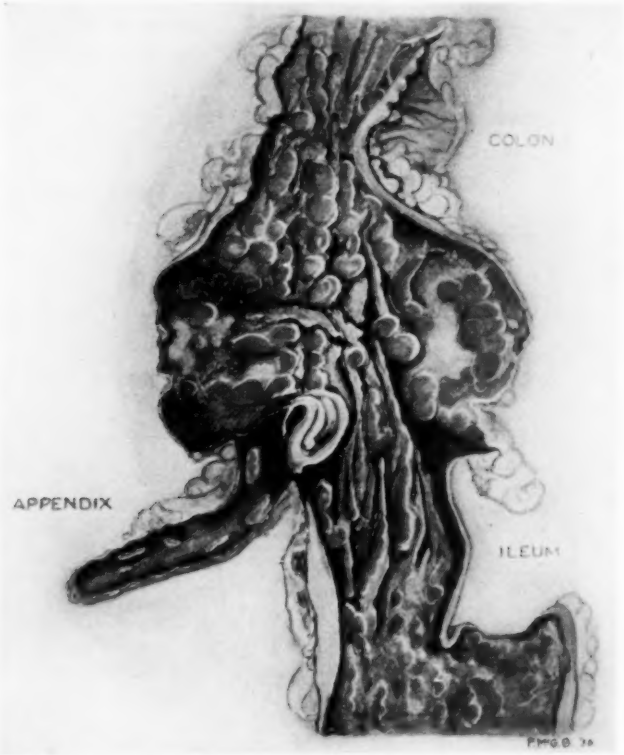

FIG. 5. Case 8, table 2. Sketch of ileocecal region. Note polypoid areas of intact mucosa, serpiginous and linear ulcerations. The process extends into the appendix. Accession No. 9273.

during outbreak in Russia in which a party of visiting scientists, including the patient, were affected. Fecal culture positive.

Case 51. Female, aged 26. Duration one-half year. Titer 1:320. Fecal culture positive. Dysentery incurred during outbreak at institution for children where patient worked as practical nurse. Her child died of acute bacillary dysentery and necropsy revealed a diffuse acute inflammation of the small and large intestines with follicular hyperplasia and necrosis and an associated mesenteric lymphadenitis.

Case 56. Female, aged 35. Duration six years. Titer 1:320. Mother, sister and brother have a similar condition but only the sister consented to examination. Titer 1:40, subdiagnostic; bacteriophage present in feces.

FIG. 6. **Case 1, table 3.** Sharply segmental and granulomatous type of distal ileitis. Accession No. 7500.

The possibility of familial contact infection is well illustrated by the following case:

Case 67. Male, aged 26. Duration 12 years. Titer 1:320. Bacteriophage present in feces. Eight others in family affected. Upon sigmoidoscopic examination two sisters showed typical lesions of chronic ulcerative colitis. One sister had a titer of 1:320 with bacteriophage present in feces. Three of her young children have had chronic diarrhea since birth, one having died of it during infancy. The other sister had a titer of 1:320. One cousin died of "intestinal hemorrhages." A grandmother and uncle have had "chronic colitis with diarrhea" for many years. No further examinations were permitted.

Case 68. Male, aged 22. Duration five years. Titer 1:160. Two sisters affected with "chronic diarrhea," one having a titer of 1:320, the other 1:160.

Case 70. Female, aged 25. Duration one year. Follow-up of Jersey City epidemic.

Case 74. Female, aged 40. Duration one year. Follow-up of Jersey City epidemic.

Case 84. Male, age unknown. Duration one year. Follow-up of Jersey City epidemic.

Case 85. Male, age unknown. Duration one year. Follow-up of Jersey City epidemic.

TABLE II

Combined Ileitis and Colitis—18 Cases

No.	Sex	Age	Duration yrs.	Agglut.	Culture	Phage	Epidemiology	Surg. Path.	Necropsy	Roent.
1	M.	17	$\frac{1}{3}$	MD 160	0	0				+
2	M.	14	$1\frac{1}{2}$	MD 160	0	0	+			+
3	M.	35	10	F 160	+F			+		+
4	F.	19	4	MD PH 160	0	0				+
5	F.	30	1	MD 160	0	0		+		+
6	F.	30	2	PH 160	0	0	+			+
7	M.	17	3	PH 160	0		+	+		+
8	M.	24	5	MD 320	0	0	+		+	
9	F.	22	$\frac{1}{2}$	PH 160						+
10	F.	23	$\frac{1}{2}$	F 320	0	0				+
11	F.	35		MD 320					+	+
12	M.	45	1	MD 100	0	0				+
13	F.	22	2	F 160	+F		+		+	
14	M.		$1\frac{1}{2}$	MD PH 320				+		
15	M.	35	2	MD 320	0	0		+		+
16	F.	35		MD PH 160				+		+
17	F.	15	$\frac{3}{4}$	MD 100	0	+			+	+
18	M.	41	$\frac{1}{6}$	F 160		+			+	

EPIDEMIOLOGICAL DATA IN CASES OF COMBINED CHRONIC ILEOCOLITIS (TABLE 2)

Case 2. Male, aged 14. Duration one and one-half years. Patient contracted the disease during an outbreak and was seen in the acute stage at which time titer was 1:640. At the end of six months the titer had dropped to 1:160.

Case 7. Male, aged 17. Duration three years. Titer 1:160. Sister has had chronic ulcerative colitis for same period. Titer 1:120.

Case 13. Female, aged 22. Duration two years. Follow-up of Jersey City epidemic. Fecal culture still positive.

TABLE III

Chronic Distal Ileitis—22 Cases

(Ulcerative or Granulomatous Type)

No.	Sex	Age	Duration yrs.	Agglut.	Culture	Phage	Epidemiology	Surg. Path.	Necropsy	Roent.
1	F.	26	1½	PH 160				+		+
2	M.	34		MD 320				+		+
3	M.	25	1½	PH 160	0					+
4	M.	45	4	MD 160	0	+				+
5	M.	57	14	F 800	0	0		+		
6	F.	28	3	MD 160				+		+
7	F.	50	5	MD PH 160				+		+
8	M.		3	MD PH 160				+		
9	M.	30	1	F 160	0	0		+		
10	M.		½	MD 160				+		+
11	M.	3½	1	SD 100	0					+
12	M.	17	⅔	PH 100	0	0		+		
13	F.	19	½	PH 100	0	0	+	+		
14	F.	20	1	F 100			+	+		+
15	F.	21	1	F 120			+	+		+
16	M.	31	10	MD 160	0			+		
17	M.	32	2	PH 160			+	+		+
18	F.	27	5½	PH 640				+		+
19	F.	19		MD 640	0			+		+
20	M.	35	7	F 100				+		
21	M.	16	6	PH F 320			+			+
22	F.	32		F 320 PH 160			+	+		

EPIDEMIOLOGICAL DATA IN CASES OF CHRONIC DISTAL ILEITIS (TABLE 3)

Case 14. Female, aged 20. Duration one year. Follow-up of Jersey City epidemic.

Case 15. Female, aged 21. Duration one year. Follow-up of Jersey City epidemic.

Case 17. Male, aged 32. Duration two years. Titer 1:160. Started during an outbreak of bacillary dysentery following banquet at hotel.

Case 22. Male, aged 16. Duration six years. Titer 1:320. Sister who nursed him had resection of ileocecal granuloma one year ago. Titer 1:320. Her husband has had chronic diarrhea and intestinal symptoms for several years. Titer 1:160.

There is a possibility that domestic animals may be the source of infection with *B. dysenteriae* in some cases. The only evidence pointing in this direction is that in three instances in this series diarrhea in a dog or cat definitely preceded the disease in the human by six to 24 hours, a common incubation period for acute bacillary dysentery.

CLINICAL

Twenty-nine instances of acute inflammation of the distal ileum were noted as an early manifestation of bacillary dysentery. These cases have been conveniently classified under the appendicular type of bacillary dysentery because of the close clinical resemblance to acute suppurative appendi-

citis.[2,3] There is a short prodromal period of nausea, headache and moderate pyrexia followed by pain and tenderness in the right lower quadrant of the abdomen. The tenderness tends to shift with change in position of the body. There is generally little or no rigidity. The spastic ileum or sigmoid may be felt. At operation, the ileum is found to be reddened, edematous and thickened, the area involved being rather sharply demarcated from contiguous healthy bowel. The vascular arborizations show intense congestion and there is a diffuse acute mesenteric and mesocolic lymphadenitis. There may be signs of an acute upper respiratory infection, particularly in the Sonne-Duval type of dysentery in children. We have not seen acute distal ileitis with mesenteric lymphadenitis in any disease other than bacillary dysentery.

The development of chronic distal ileitis from the acute form of the disease in the same individual has been seen in 14 instances. (Table 2, cases 1, 2, 5, 9, 10, 11, 12, 13; table 3, cases 10, 11, 12, 13, 14, 15.) The development of chronic ulcerative colitis following an attack of acute bacillary dysentery in the same individual has been seen in 25 instances. (Table 1, cases 11, 18, 21, 22, 29, 33, 38, 39, 40, 41, 43, 44, 45, 46, 51, 56, 58, 61, 62, 70, 72, 77, 81, 84, 85.) There is not always a clear line of demarcation between the ileitis and colitis group since bacillary dysentery affects both the small and large bowel simultaneously. Usually, the ileum or colon alone is affected in the chronic form of the disease, but the ileocecal valve does not necessarily limit the extent of the lesion. Although the transition stages from acute bacillary dysentery to chronic ileitis or ulcerative colitis were first noted in sporadic cases, perhaps the best illustration is offered in the follow-up studies of the Jersey City epidemic.[4] Of an original group of 210 hospitalized patients 122 were re-studied nine to 12 months later. Forty-six of these patients (37.7 per cent) had persistent or recurring intestinal symptoms or signs, viz.: eight (6.5 per cent) had diarrhea with blood, mucus and pus; 12 (9.8 per cent) had a watery diarrhea without gross blood; three (2.4 per cent) had bloody evacuations without diarrhea and 23 (19 per cent) had miscellaneous intestinal disturbances such as recurring attacks of abdominal cramps. In the above group of 46 patients roentgenographic evidence of chronic ulcerative colitis was obtained in eight, sigmoidoscopic proof in two, specimens showing chronic distal ileitis were obtained at operation in two cases and necropsy in one. Thus visible evidence of chronic distal ileitis or ulcerative colitis was obtained in 13 (10.7 per cent) of a total of 122 patients nine to 12 months after the initial attack of bacillary dysentery or roughly one out of every 10 patients. It is possible that these figures would have been higher if routine roentgenographic examinations had been made in every return study.

Abortive and atypical types of acute bacillary dysentery have been recently encountered.[1,5] They are frequently unrecognized clinically or incompletely studied in the laboratory. In the asymptomatic form, epidemic type, the fecal cultures are positive and intestinal lesions are seen through

TABLE IV

Follow-up Studies of Jersey City Epidemic of Bacillary Dysentery

Total number of hospitalized cases	210
Total number of follow-up cases	122
(*a*) Roentgenographic evidence of chronic ulcerative colitis	8 (6.5 per cent)
(*b*) Additional cases with sigmoidoscopic evidence of chronic ulcerative colitis	2 (1.7 per cent)
(*c*) Chronic distal ileitis (two at operation, one at necropsy *)	3 (2.5 per cent)

* Almost entire ileum and all of colon involved.

Proof of chronic ulcerative colitis or ileitis nine to 12 months after the onset of acute bacillary dysentery (Flexner)—10.7 per cent (13 out of 122, or approximately 1 : 10).

the sigmoidoscope, but the patients have no complaint. The organisms disappear in a week to 10 days and the lesions heal shortly thereafter. These patients are discovered only in the course of epidemiological surveys. In the afebrile type the clinical course is typical except for a normal or almost normal temperature. In the constipated type, a bowel movement may not occur for three or four days. This occurs in individuals who usually have one or two normal bowel movements a day. Sometimes a single watery stool is noted at the onset of the disease. Constipation is a frequent symptom in acute bacillary dysentery immediately following the acute stage (seven to 10 days) and suggests Nature's effort at splinting the bowel to favor healing. The meningitic form suggests an acute meningococcus meningitis, but lumbar puncture reveals a clear fluid, normal cytology, the presence of sugar, no globulin and negative culture. Every patient seen thus far has had an associated labial or nasal herpes. Diarrhea usually ensues shortly after the onset of meningitic symptoms. The appendicular form has already been described under acute distal ileitis. Three cases of the agranulocytoid type have been seen, the blood picture bearing a very close resemblance to that seen in agranulocytosis. This phenomenon will be referred to again in connection with the myelotropic toxin.

In chronic ulcerative colitis and ileitis " mendicant's posture " has been frequently encountered. This term is applied to a peculiar position of the body and a characteristic gait seen in ambulatory patients during the period of acute exacerbation of intestinal symptoms. It disappears completely during the remission stage. The patient is generally quite emaciated and dehydrated from frequent watery evacuations. His pallor, hollowed cheeks and sunken temples form an almost funereal background to an expressionless face, or to a worried look which betokens great physical discomfort. In walking there is exhibited a peculiar shuffling gait, the cervical and dorsal spine being bent forward and held quite rigid. The shoulders are high, the head is bowed and the abdomen somewhat concave. The patient appears to be looking at the ground and only casually glances upward at passersby without moving his head. One hand is held on the mid-section or is placed upon the hip. It seems as though only a distaff would be required to complete a picture of the proverbial beggar. It is apparently a natural position

for these patients who suffer from almost constant cramps or abdominal soreness.

Serology

Diagnostic, agglutination titers against *B. dysenteriae* were obtained in 22 cases of chronic distal ileitis, 18 cases of combined ileocolitis and 76 cases of chronic ulcerative colitis, or in 116 (93.5 per cent) out of a total of 124 cases. Of the eight cases in which the titers were not done or found to be at the subdiagnostic level, one (case 29, table 1) had a positive fecal culture, three (cases 38, 39, 61, table 1) were originally seen in the Jersey City epidemic and the remaining four (cases 20, 25, 50, 71, table 1) were negative for all bacteriological or serological evidence of bacillary dysentery. All of the chronic cases included in this study were clear cut examples of the disease diagnosed by the usually accepted criteria noted under "Diagnosis." Supplementary data were furnished by pathological study of operative or necropsy specimens. In the serological examinations 18-hour viable broth cultures, the gross test tube method, four hours incubation at 55° C. and refrigeration overnight were used. Control agglutination studies of 300 patients from the same area showed diagnostic titers in only 4.6 per cent for all types except *B. dysenteriae Sonne-Duval.*[6] In the latter no positives were obtained. Titers of 1 : 100 or over were regarded as diagnostic in all except the Sonne-Duval type in which 1 : 50 or over was considered positive.* Most of our acute mild Flexner and Sonne-Duval infections gave only transitory titers. Hiss[7] calls attention to the frequent occurrence of weak agglutination titers in bacillary dysentery. It suggests the possibility that a negative titer in chronic ulcerative colitis or ileitis may be inconclusive. In further support of this contention additional evidence is furnished by follow-up titers nine to 12 months after the Jersey City epidemic in 106 cases. Thirty-two (30 per cent) showed a diagnostic titer and 74 (70 per cent) a subdiagnostic or negative titer. Of 11 patients who developed chronic ulcerative colitis or ileitis, eight (73 per cent) showed a follow-up diagnostic titer (table 1, cases 21, 44, 70, 74, 84; table 2, case 13; table 3, cases 14 and 15); one (9 per cent) showed a negative titer (table 1, case 38); the remaining two (18 per cent) not having been tested (table 1, cases 39 and 61).

In some cases peculiar cross agglutination titers were obtained in the chronic stage. Cases 21 and 70, table 1, in which original titers of 1 : 120 against the Flexner organism were found during the epidemic, showed only 1 : 40 against the same organism at the end of one year, but a titer of 1 : 100 against the Mt. Desert and Park-Hiss strains. These results are probably

* There is a lack of unanimity of opinion with regard to diagnostic titers in bacillary dysentery. A *rising* agglutination titer in acute bacillary dysentery is diagnostic, but in some cases it may not go beyond 1 : 100. The low titers (1 : 50) obtained in Shiga-Kruse or Sonne-Duval infections have been repeatedly shown by other investigators. As in the chronic forms of the disease agglutination titer is to be regarded as only one link in the chain of evidence. It should be used only in conjunction with epidemiological, clinical, pathological, bacteriological and roentgenographical studies.

due to the antigenic heterogeneity of the Flexner group. The Flexner organism is said to contain at least four antigenic components, V–W–X and Z,[8] which are present in every strain but with one component predominating over all the others. Ordinarily this is sufficient to stamp a given organism as a definite type serologically. In *B. dysenteriae Flexner Y,* however, the antigenic components are more evenly balanced and the serum prepared against it has a more irregular and wider range of agglutination against other members of the Flexner group. Owing to the many variants of the Flexner organism a sufficient number of smooth, agglutinable strains should be used, particularly those prevalent in the area in which the studies are being conducted. The Jersey City, Mt. Desert and Park-Hiss strains are always included in our routine set-up. In actual practice, it appears that it is chiefly the severe cases of acute bacillary dysentery or patients with residual infections who develop the chronic lesions. Follow-up agglutination studies of patients who had acute distal ileitis which healed completely, as shown by clinical and roentgenographic examinations, revealed a marked drop in titer at the end of six to 12 months, sometimes to a sub-diagnostic level.

Bacteriology

It is generally accepted that positive fecal cultures in acute bacillary dysentery are usually not obtained after the first or second week. Repeated and persistent cultural examinations of the feces or intestinal mucosa in chronic ulcerative colitis and ileitis were positive for *B. dysenteriae* in 10 cases out of 70 cultured (14.2 per cent), viz.: table 1, cases 11, 18, 29, 40, 48, 49, 51, 76; table 2, cases 3 and 13. In one instance of chronic distal ileitis the organism was recovered approximately one year after resection of the distal portion of the ileum.

Bacteriophage was found in 20 (39.2 per cent) out of 51 cases examined, viz.: table 1, cases 5, 8, 9, 10, 13, 16, 30, 40, 43, 54, 55, 59, 65, 67, 71, 72, 78, 83; table 2, case 17; table 3, case 4. It appeared to be group rather than type specific and, when taken in conjunction with other findings, of definite value in diagnosis. In the examination of 100 normal controls, bacteriophage was present in one fecal specimen.

The more often fecal and sigmoidoscopic cultures are repeated, the higher will be the percentage of positive findings. Fresh mucosal scrapings with a dull curette or crypt aspirations are better for culture than feces. For aspiration a heavy walled capillary tube is used (5 mm. outside diameter, 35 cm. long). A fusiform dilatation, sufficient to hold three or four drops of fluid, is blown into the tube about 2 cm. from the distal end which is bent slightly for better approximation to the bowel wall. This inexpensive device, prepared in the laboratory, is inserted through a 12 inch sigmoidoscope, the mucosal aspiration is made by sight and the material seeded directly on a fresh Endo plate. A small one and one-half inch rubber bulb without a valve, but with a hole at the bulbous end is used for

aspiration. The bulb is squeezed and the index finger then placed over the hole before suction is started. This affords excellent control with a minimal amount of positive pressure in the capillary tube. The dilated portion holds sufficient fluid for culture, warm stage and wet smear-iron hematoxylin examinations for *Endameba histolytica.*

Positive culture of *B. dysenteriae* in chronic ulcerative colitis and ileitis is neither an incidental and irrelevant finding, nor is it indicative of a healthy carrier. Our experience has been that these patients have never fully recovered from the original attack of bacillary dysentery and that careful physical, roentgenographic and sigmoidoscopic examinations always reveal intestinal lesions. Control studies in more than 300 cases failed to reveal *B. dysenteriae* in the feces of individuals free of all manifestations of the disease. Our experience in bacillary dysentery points to the existence of "sick carriers" rather than "healthy carriers." In cases 11, 29, 40 and 49, table 1, there were no intestinal or other physical complaints in remission periods nor was an organic lesion suspected by the referring physicians. Yet *B. dysenteriae* was recovered in each instance, sigmoidoscopic evidence of ulceration was present and was corroborated in three cases by roentgenographic examinations. In two hospital outbreaks in New York City (Sonne-Duval and Flexner Y) the children were at first regarded as carriers or the cultures considered as merely incidental findings. Bloody diarrhea in a child who appeared quite well and who had no particular complaints or pyrexia did not correspond to the orthodox picture of acute bacillary dysentery. Necropsy findings and epidemiologic surveys revealed the true nature of the disease. It recalls to mind the sudden deaths occasionally seen in Sonne-Duval dysentery.

Experimental and clinical studies suggest that the primary intestinal lesions in acute bacillary dysentery are due to a thermostabile endotoxin which is excreted from the blood vessels through the wall of the bowel into the lumen. Flexner [9] called attention to this important mechanism in 1906, stressing toxin excretion rather than the local action of the organism itself as being the cause of the intestinal ulcers. Zinsser [10] described typical diarrheal and nervous symptoms following the intravenous injection of large doses of toxin into rabbits. We have repeatedly failed to infect rabbits by the oral route, but have readily produced diarrhea and intestinal lesions by the intravenous injection of the living organisms or toxin. These organisms have been recovered under proper control conditions from the feces of rabbits 24 to 48 hours after the intravenous injection of 18-hour broth cultures.

Re-absorption of toxin from the intestine occurs, producing a vicious cycle in the severe toxic cases. The major pathologic changes in acute bacillary dysentery are usually produced within the first 24 to 48 hours. There are probably a number of toxins produced by *B. dysenteriae.* Besides the enteric toxin and thermolabile neurotropic exotoxin, described by Olitsky and Kligler,[11] there also appear to be arthritic and myelotropic toxins

which have an affinity for the joints and bone marrow respectively. The incidence of arthritis in both acute bacillary dysentery and chronic ulcerative colitis is quite high. Our figure for the latter is 15.4 per cent (table 1, cases 2, 3, 6, 8, 10, 12, 13, 14, 17, 24, 26, 27, 30, 49, 54, 66, 67, 82; table 2, case 6. Nineteen cases of a total of 124). The larger joints were more commonly affected, particularly the wrists, knees or ankles. Individual fingers or toes were involved less frequently. The exacerbation and remission of joint symptoms corresponded to the alternating periods of recrudescence and subsidence so characteristic of chronic ulcerative colitis and ileitis. Roentgenograms taken during the acute stage of arthritic symptoms revealed peri-articular inflammation in two cases (table 1, cases 10 and 26). The intradermal injection of 0.1 c.c. dysentery toxin (approximately 1 M.L.D. white mouse) produced a sudden and marked flare-up of joint pains in many instances. This was particularly noteworthy in case 30, table 1, the patient requiring morphine for relief.

The only evidence suggesting a myelotropic toxin is the frequency of leukopenia and the occurrence of three instances of marked fulminating neutropenia resembling agranulocytosis in acute bacillary dysentery.[12] The toxin appears to affect the endothelium of the bone marrow sinusoids preventing the migration of granulocytes from their extra-vascular zone of formation into the circulating blood. Pathologic study reveals no deficiency in leukopoiesis or erythropoiesis in the marrow.

The secondary intestinal lesions are essentially intramural infections with the enterococcus, and hemolytic and non-hemolytic *B. coli*. These organisms gain entrance through the denuded intestinal mucosa, advance along the lymphatic pathways and are persistent and difficult to eradicate. Sudden, spontaneous remissions in chronic ulcerative colitis seem to be due to an increase in the immunity defense mechanism. Preliminary studies point to an increase in the agglutination and bactericidal titers of the blood during the remission stage. Recurrence of symptoms follows a lowering of this defense mechanism so that chronic ulcerative colitis or ileitis is often a cyclic disease corresponding to alternating periods of relatively high and low degrees of immunity. A knowledge of this natural trend should govern the evaluation of any given form of therapy.

The enterococcus and *B. coli* have been isolated from intramural abscesses and secondary lesions of the renal pelvis. Aspirated fluid from inflamed joints in acute bacillary dysentery, chronic ulcerative colitis and ileitis has proved persistently negative upon culture. Secondary toxin absorption effects may be present due to the presence of toxic anerobes such as *B. welchii* in the bowel. This factor should be borne in mind in connection with intestinal oxygenation.[13]

Pathology[14]

In order to understand the pathological lesions in chronic ulcerative colitis and ileitis, it must be remembered that any part of the small or large

intestine may be involved during the stage of primary infection with *B. dysenteriae.* "Skip" areas of segmental involvement may occur. The small and large intestine may be affected independently or concomitantly. In the former, the distal portion of the ileum is usually involved and in the latter, all or part of the large intestine including the appendix. In every case thus far studied sigmoidoscopic examination revealed acute lesions so that it may be stated that in the acute stage of bacillary dysentery the rectosigmoid is always involved. Repeated sigmoidoscopic examinations starting within a few hours after the onset of symptoms indicate the earliest lesion to be a hyperplasia of the solitary acuminate lymph nodules which are affected in a multiple and punctate fashion. There is an acute diffuse inflammation of the overlying mucosa which is covered with a mucoid, blood-tinged or purulent exudate. Bleeding occurs after the slightest trauma such as passage of the sigmoidoscope or use of a dull culture curette. Follicular necrosis quickly ensues, but "weeping" of blood appears to take place even before superficial ulceration is evident. Studies at this stage were supplemented by necropsies on infants. The solitary acuminate lymph nodules are in various stages of hyperplasia and necrosis, the overlying mucosa being ulcerated and the necrotic lymph nodules appearing like the mouths of tiny diverticula. In the severe cases the entire lymph nodule is eventually destroyed. Adjacent areas of necrosis and ulceration coalesce, thus adding width and depth to existing ulcers. The necrotic mucosa is bordered by a marginal zone of polymorphonuclear leukocytes, some lymphocytes and plasma cells. Necrosis of the submucosal blood vessels underlying the ulcerated area occurs and is probably due to the dysentery toxin. The vessel wall ruptures and releases its contents into and through the ulcer. An intense vascular congestion is present throughout this period. In fatal cases serpiginous and geographic areas of denudation occur, the acute inflammation permeates the entire intestinal wall and death occurs from intense toxemia or perforation or both. This process generally takes about two to four weeks in adults in the Flexner and Sonne-Duval types of dysentery seen in the New York area. In infants, death is usually due to toxemia and dehydration which are apt to prove fatal within a few days to one week.

If one can judge from the follow-up figures of the Jersey City epidemic approximately 90 per cent of the cases of acute bacillary dysentery recover completely. The other 10 per cent recover partially or temporarily only to suffer periodic exacerbations and remissions every few weeks or months. In these cases the acute lesions do not heal. Ulcerations persist and spread and secondary intramural infection occurs. That this process is merely a perpetuation of the acute dysentery is borne out by repeated follow-up examinations which prove that neither have the intestinal ulcers healed nor have the symptoms ever cleared up. The disease has reached the chronic phase and whether the process is confined to the ileum or to the colon, the pathologic process is essentially the same. Mural fibrosis ensues and represents an attempt at healing. The lymph nodules are destroyed. Here and

there islands of mucosa may remain intact and often, due to the blockage of ducts by scar tissue and the accumulated secretion, may take on a polypoid appearance. In the ileum or cecum particularly, a granulomatous lesion may be encountered.[15] It merely represents a productive type of inflammation. The presence of giant cells may suggest tuberculosis, but specific stains and guinea pig inoculations with the macerated tissue always prove negative. In general, the end result is an ulcerated, narrowed, thickened, infected, vascularized tube of connective tissue. This is the late stage of bacillary dysentery, perhaps more generally termed chronic distal ileitis, non-specific granuloma, and chronic ulcerative colitis. The pathological changes above described account for the roentgenographic findings in these diseases, viz.: Kantor's string sign of chronic distal ileitis,[16] obstructive lesions at or near the ileocecal region (granuloma), irregularities of mucosal pattern (ulceration), loss of haustration, narrowing of the large bowel or polyposis. Fistulous tracts and secondary extramural abscesses occur as complications due to extension of the infection through the wall of the bowel. Fortunately the process is often a comparatively slow one so that when perforation does take place there is a well walled off area of inflammation which prevents a diffuse peritonitis.[17] Residual infections with *B. dysenteriae* may occasionally be found in the mesenteric or mesocolic lymph nodes.

Pathological Reports. Following is a brief summary of the relevant surgical pathology or necropsy findings in individual cases:

Chronic Ulcerative Colitis (table 1).

Case 8. Ulceration, intramural infection with fibrosis of the cecum and ascending colon. (Surgical resection.)

Case 45. Ulceration, intramural infection with fibrosis and polyposis cystica of the ascending, transverse and descending colon. Perforation of sigmoid. (Necropsy.)

Case 55. Ulceration, intramural infection with focal abscesses, polyposis cystica of entire large bowel. Beginning perforation in sigmoid. (Necropsy.)

Combined Ileitis and Colitis (table 2).

Case 3. Obstructing granuloma 10 cm. of distal ileum. (Surgical resection.) "Skip" type of lesion in colon. (Postoperative study.)

Case 5. Ulcerative, non-stenosing type of ileitis involving 10 cm. distal ileum. Chronic ulcerative colitis. (Laparotomy without resection.)

Case 7. Ulcerative and productive type of distal ileitis involving 12 cm. of ileum (partial resection). Chronic ulcerative colitis of the cecum and ascending colon (postoperative study).

Case 8. Ulceration, mural fibrosis and polyposis of the distal 30 cm. of ileum, appendix and entire colon. (Necropsy.)

Case 11. Approximately the distal half of ileum and entire colon were the seat of innumerable discrete and confluent ulcers with many areas of low grade local peritonitis. Perforation of sigmoid. (Necropsy.)

Case 13. Ulceration, mural fibrosis and polyposis of entire colon, perforation of sigmoid. Early granulomatous lesion distal 10 cm. of ileum. (Necropsy.)

Case 14. Segmental involvement of ileum approximately 60 cm. from ileocecal valve, intramural infection with several sinuses connecting adherent ileum

and cecum. Chronic ulcerative disease with mural fibrosis of ascending colon. (Surgical resection.)

Case 15. Chronic ulcerative lesion of distal ileum, with polyposis cystica in proximal colon to splenic flexure. "Skip" lesion in upper sigmoid. (Surgical resection.)

Case 16. Segmental ulcerative and productive type of ileitis 20 cm. above ileocecal valve. Similar lesions in appendix, cecum and proximal portion of ascending colon. (Surgical resection.)

Case 17. Serpiginous and geographic ulceration with intramural infection from ileocecal valve to anus. Many ulcers in healing stage located in distal 40 cm. of ileum. (Necropsy.)

Case 18. Ulcerative ileocolitis involving almost entire ileum, the appendix and colon. Polyposis cystica coli with perforation in transverse colon.

Chronic Distal Ileitis (table 3).

Case 1. Segmental granulomatous type of inflammation involving ileum for a distance of 10 cm. at a point approximately 15 cm. above ileocecal valve. (Surgical resection.)

Case 2. Stenosing, cicatrizing lesion of distal 10 cm. of ileum. (Surgical resection.)

Case 5. Ulceration with extensive mural fibrosis and stenosis distal 30 cm. of ileum. (Necropsy.)

Case 6. Ulceration with extensive mural fibrosis and stenosis of distal 35 cm. of ileum. (Surgical resection.)

Case 7. Thickening and linear ulceration of distal 5 cm. of ileum. (Surgical resection.)

Case 8. Involvement of several loops of ileum which were adherent to one another, with several sinus tracts between coils of intestine and mesentery. Abscess in pelvis. (Surgical resection.)

Case 9. Chronic non-obstructive distal ileitis (10 cm.) with diffuse mesenteric lymphadenitis. (Laparotomy without resection.)

Case 10. Distal 15 cm. of ileum involved. Extensive intramural infection, fibrosis with stenosis. (Surgical resection.)

Case 12. Distal 12 to 15 cm. of ileum thickened, inflamed. Mesenteric lymphadenitis. (Laparotomy without resection.)

Case 13. Distal 10 cm. thickened and inflamed. No evident stenosis. (Laparotomy without resection.)

Case 14. Distal 40 cm. of ileum thickened, stenosed and inflamed. (Surgical resection.)

Case 15. Distal 20 cm. of ileum involved. Intramural infection and fibrosis. Mesenteric lymphadenitis. (Surgical resection.)

Case 16. Distal 30 cm. of ileum involved. Coils adherent with formation of two fistulous tracts. Ileocolic fistula and abscess. (Surgical resection.)

Case 17. Involvement of 37 cm. of ileum at a point 50 cm. above the ileocecal valve. Inflamed loops adherent, thickened and covered with plastic exudate. Mesentery thickened and adherent. Productive, granulomatous type of inflammation with obstruction. Adjacent portions of intestine exhibited old ulcers. (Surgical resection.)

Case 18. Cicatrizing obstructive lesion distal 15 cm. of ileum. (Surgical resection.)

Case 19. Granuloma distal 7 cm. of ileum causing almost complete obstruction. (Surgical resection.)

Case 20. Thickening and inflammation distal 15 cm. of ileum. Mesenteric lymphadenitis. (Resection not done.)

Case 22. Granulomatous, obstructive lesion distal 10 cm. of ileum. (Surgical resection.)

Roentgenology

Roentgenographic evidence of chronic ulcerative colitis or ileitis was obtained in 84 cases examined. In 60 cases, only the colon was involved, all or in part; in 14 both the distal ileum and colon were involved and in 14 only the ileum was affected. The roentgenographic findings did not always correspond to the surgical pathology or necropsy findings. In the latter, particularly, the lesions found were more extensive than those visualized in the roentgenogram. In some cases the development of the chronic lesions could be traced roentgenographically.

Case 34, Table 1. Onset of the disease in 1932. At this time roentgenographic study of the intestinal tract proved negative. In April 1935, the films revealed chronic ulcerative colitis with polyposis cystica.

Case 66, Table 1. At onset of the disease in 1931 roentgenographic examination was negative. In June 1935, the pictures revealed chronic ulcerative colitis involving the entire large intestine.

Case 79, Table 1. At onset of the disease in 1935 no lesion was noted, but in April 1936, the cecum and ascending colon were involved.

Case 2, Table 2. At onset of the disease in December 1934, there was no evidence of ulcerative colitis. In May 1936, the ileum and entire colon were involved. This patient was observed clinically during both the acute and chronic stages.

Diagnosis

The diagnosis of a typical case of acute bacillary dysentery is usually quite simple. A history of contact infection, a prodromal period of 12 to 48 hours of malaise, headache, anorexia and nausea, accompanied by a moderate elevation of temperature is followed by a profuse, watery diarrhea. The fever increases, cramps and tenesmus are marked and mucus, pus or bright red blood appears in the feces. Sigmoidoscopy reveals an intense acute inflammation with ulceration of the mucosa. The tender, spastic ileum and sigmoid can be felt through a thin abdominal wall. A leukopenia is often present at the onset of the disease and may continue throughout. Different strains of the same organism (e.g. Flexner) behave differently in this regard suggesting the presence or absence of a specific myelotropic toxin. Positive fecal cultures are usually obtained during the first week after which the bacteriophage and agglutination titer increase. The atypical forms of acute bacillary dysentery recently encountered include the afebrile, asymptomatic, constipated, appendicular, meningitic, agranulocytoid and Sonne-Duval. Outbreaks of Sonne-Duval dysentery have been recognized in the United States only in recent years. The child with bloody, diarrheal stools who may not appear to be ill should be isolated at once and studied intensively for *B. dysenteriae*. Contact cases of this type on hospital wards are relatively frequent and the outbreak may die out before delayed studies are completed.

The diagnosis of chronic dysentery is more difficult, particularly if the patient is seen for the first time one or more years after the initial infection. The diagnostic criteria in chronic distal ileitis, non-specific granuloma and chronic ulcerative colitis may be summarized as follows:

(*a*) Epidemiologic: History of contact infection at the time symptoms *first* appeared.

(*b*) Clinical: Persistent or recurring attacks of abdominal cramps and diarrhea; sigmoidoscopic evidence of ulceration, pseudo-polyposis or mural fibrosis with stenosis; palpation of tender, thickened or spastic ileum or sigmoid; mendicant's posture on standing or walking [18]; chronic arthritis, the exacerbations being associated with periodic attacks of diarrhea.

(*c*) Roentgenographic: Defects in the mucosal pattern; loss of haustration; narrowing of the bowel lumen; presence of the string sign; intrinsic obstructive lesion (granuloma).

(*d*) Laboratory: Culture of *B. dysenteriae* from crypt aspirations or mucosal scrapings; diagnostic bacteriophage in the feces; diagnostic agglutination titer of the blood. The skin test and intestinal smears for cytology may be used as supplementary aids in diagnosis.

Differentiation from amebic dysentery [19] may be made as follows: In acute amebic dysentery the ulcers are discrete, undermined and often surrounded by a hemorrhagic halo. The intervening mucosa is not as acutely inflamed as in bacillary dysentery, but the late lesions of both diseases may be indistinguishable from one another through the sigmoidoscope. In amebic dysentery the ileum is not involved, the trophozoites can be detected in the diarrheal discharge and together with the cysts may often be recovered in the mucosal scraping or biopsy. The therapeutic test with emetine or a suitable substitute is a good one. The same may be said of the oxygen test, for after intestinal oxygenation the amebae appear in great numbers due to their avidity for oxygen. In amebic liver necrosis oxygen has a similar effect, the protozoa emerging quite rapidly from the wall and appearing in the drainage tube. Wet smear fixation in Schaudinn's fluid followed by the iron-hematoxylin stain should supplement all warm stage examinations. Double infections with *B. dysenteriae* and *B. typhosus* or *B. dysenteriae* and *Endameba histolytica* do occur since they generally have a common source. We have had two cases of each. This possibility should be borne in mind when patients are unusually refractory to treatment.

Therapy

The ideal therapy of chronic distal ileitis, chronic non-specific granuloma and chronic ulcerative colitis *is the prevention of bacillary dysentery.* The typical and atypical forms must be recognized by the family physician and the patients promptly isolated. Every case of diarrhea, particularly in hos-

pitals and other institutions, should be isolated at once without waiting for the laboratory reports. No harm is done if the bacteriologic findings prove negative and this simple precaution may save the lives of many infants. Basically, it is a public health problem to be solved ultimately with the aid of adequate funds for disease prevention.

There must be stricter supervision of food-handlers, water supply and sewage disposal on land and on board ships. There must be complete freedom from political and business control, both of which foolishly perpetuate the very disease regarding which publicity is shunned. Prophylactic vaccination against *B. dysenteriae* during small outbreaks or epidemics is advisable, as indicated by experimental work on animals. Strains of relatively low toxicity may be used.

In acute bacillary dysentery, a potent dysentery antitoxin must be given within the first 24 to 48 hours to be most effective as the major damage is usually done during that period. It may be supplemented by the liberal use of castor oil in humble imitation of Nature's effort to rid the body of specific toxins and bacteria. Normal saline or 5 per cent glucose in saline should be used freely where indicated by hypodermoclysis or intravenously. Every patient with acute bacillary dysentery should be followed up for one year in order to safeguard him against the chronic lesions. Any patient with acute bacillary dysentery which lasts more than three weeks is a potential case of chronic ulcerative colitis or ileitis and should be treated as such.

In the chronic forms of dysentery active immunization may be effected by the use of D–C vaccine and D–C antivirus (the D–C referring to polyvalent strains of *B. dysenteriae, Enterococcus,* hemolytic and non-hemolytic *B. coli*).[20] Except during temporary acute exacerbations a high caloric, high vitamin diet should be used. Limitations based upon minimal residues are of doubtful value. It must be remembered that most of the small bowel is still functioning well. Intestinal oxygenation is used to control the anerobes whose toxins are absorbed through denuded areas, to promote drainage of aerobes from the interstices of the intramural structures and to quiet excessive intestinal peristalsis. Oxygen also serves as an efficient deodorizer of the foul discharges so commonly encountered. Surgical resection, except as an emergency procedure, is contraindicated as the operator generally cuts through infected bowel wall or overlooks "skip" areas with the result that recurrences are common. Repeated transfusions are valuable, particularly if recovered cases of chronic dysentery are used as donors. Professional donors are now being tested in order to determine specific blood agglutinins against *B. dysenteriae.* Those showing diagnostic titers are used for patients ill with acute or chronic bacillary dysentery, subject to the usual preliminary tests for grouping, cross matching and syphilis. Such transfusions have the advantages of blood from a homologous species in lessening serum reactions and supply both fluid and cells to combat dehydration and hemorrhage. They may be repeated as often as necessary and

preferably given by the direct method. The routine use of emetine to guard against a co-existing amebic dysentery is advisable.

Summary

A correlated study of 553 cases of acute bacillary dysentery, acute and chronic distal ileitis and chronic ulcerative colitis points to their common pathogenesis. The development of the different stages has been seen in individual cases including those seen in a major epidemic. Attention is called to the absence of diagnostic agglutination titers in many recovered cases of acute bacillary dysentery and in some cases of chronic dysentery. Control studies and search for other primary etiologic factors proved negative. Secondary factors influencing the course of the disease or present as the result of it were considered as not falling within the scope of this paper. The close association of acute bacillary dysentery and the group of chronic diseases above mentioned appears to be too constant to be regarded as other than of etiologic significance.

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THE HISTORY OF HOSPITALS, WITH SPECIAL REFERENCE TO SOME OF THE WORLD'S OLDEST INSTITUTIONS *

By HENRY R. CARSTENS, M.D., F.A.C.P., *Detroit, Michigan*

AMONG the living institutions established by man, few have enjoyed a longer or more honorable history than hospitals. In very early documents, institutions are mentioned which may well be the prototypes of our modern hospitals. Such establishments were known in Ceylon, in India (for animals, as well as man), in Greece (in connection with some of the temples), and even in Ireland. With the exception of some of those in India, none are known to have existed for very long, at least not into the modern times.

As Christianity spread through Europe, a practical manifestation of its charitable teachings was the establishment of various institutions for the care of the pilgrim, the wayfarer, the aged, the ill, and the infirm. In medieval times, their number increased rapidly, impetus being given to the movement by the Crusades (in the twelfth century), and by the spread of leprosy and the plague (in the twelfth to the fifteenth centuries). Limited though these establishments were, according to our modern standards, some of them attained a remarkably high efficiency for the times. Following the subsidence of the epidemics most of these institutions disappeared, and in general, hospital practice sank to rather low standards for many centuries until it rose to new heights during the past hundred years.

The word " hospital " is derived from the Latin, " hospitium "—a guest, as the institutions were first designed for the reception of wayfarers, pilgrims, and the infirm. Almost all were established by the church, although in England in later medieval times they were often founded by private benefaction, and in Germany quite frequently as municipal undertakings. Even in these cases, they were usually placed under the direction of a local church or monastery.

The oldest hospitals still in existence are the Hotels Dieu in Lyons and Paris, in France. Earliest mention is made of the Hotel Dieu in Lyons in a manuscript of 580 A.D., in which its establishment by Childebert is recorded. This is the oldest hospital which has continued in existence with the same name and the same purpose, its life having now spanned a period of almost fourteen centuries. A number of similar institutions were built in the seventh and eighth centuries at Poitiers, Verdun, Arles, Milan, and elsewhere, but their life was comparatively short. At about this time, leprosy commenced spreading through the European continent, and many institutions were established for the reception of lepers. The term " leprosy " was then a rather inclusive term, including probably a number of different diseases, such as lupus and scrofula, as well as leprosy. The lot of the leper

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in those days was a hard one, outcast from society, bereft of all rights as a citizen, he had no means of making a livelihood. It was natural then to establish places for his care, although these were hardly hospitals, but really places for segregation.

Gradually these institutions tended to develop into different types, certain ones being designated for the care of the sick, the blind, the aged, orphans, lepers, etc. In the course of time the need for some of these became less, and those which are still existent usually belong to one of two general types, first, the almshouse for the care of the aged and indigent, and second, the hospital as defined in the modern sense.

The spread of hospitals was most rapid at the time of the Crusades, when large groups of individuals were moving by various routes to the Holy Land. Great encouragement to the foundation of hospitals was given by Innocent III, to whom is due the establishment of the Order of the Holy Ghost. In about the year 1204, the Pope founded the Ospedale di Santo Spirito at the old Tiber bridge in Rome. Hearing of the efficiency of the Hospital at Montpellier in France conducted by Guy de Montpellier, the Pope sent for him and entrusted him with the directorship of the Order of the Holy Ghost. Under Guy de Montpellier's guidance, the Order administered a tremendous number of hospitals throughout Europe, either starting these as new institutions, or taking over the management of hospitals previously established. It has been estimated that almost two thousand were founded in Germany, and probably a greater number in France. A number of these still remain, although the Order gradually declined, being active now only in Italy. Other orders also participated in this movement, especially the Teutonic Order, the Johanniten, and the Order of the Lazarites, the last named devoting itself more particularly to the care of lepers. The brilliant history of the Order of St. John at the time of the Crusades is also noteworthy. The Hospital of St. John in Jerusalem (1099) had a high reputation as an institution of the first rank.

In Islam also, many hospitals were established during the time that the Arabians were spreading their culture through a rapidly extending territory. The Arabians' medical inspiration came largely from the Persian hospital in Djoundisabour (sixth century), at which many of them studied. Returning to their homes they founded institutions which were remarkably well organized for the times. A large number of these hospitals (called "bimaristans") were established at Bagdad, Damascus, Cairo, Aleppo, and elsewhere. There were often separate wards for the specialties (particularly ophthalmology and orthopedics), and provision was made for ambulant patients. A regular staff was in attendance, and the teaching of students was well organized.

In the course of time, there were many changes in fortune and development among the early institutions. The great majority have disappeared. Some have lost their buildings, and persist now only as endowments, or as place names, others have lived through the centuries. Some are very modest

and hardly worthy of their names. Others, proud of their heritage, are among the foremost European institutions. Some of these will be considered in the following paragraphs. The list does not pretend to be complete, it includes more particularly those which are of interest at the present time.

By way of comparison, it may be of interest to note that the western hemisphere has a number of hospitals which date back to early colonial times. The oldest of these is the Hospital of the Immaculate Conception in Mexico City, established in the early 1500's. In Canada, the oldest are the Hotel Dieu du Précieux Sang in Quebec (1639), and the Hotel Dieu de St. Joseph in Montreal (1644). In the United States, the first hospital founded as such was the Pennsylvania Hospital in Philadelphia (1751). There are a number which were established as almshouses or workhouses at an early date, the Philadelphia General Hospital (1751), Bellevue Hospital in New York (1735), the Charity Hospital in New Orleans (1736). These all became hospitals some decades later. In the Philippines, the Hospital de San Juan de Dios was founded in 1596 in Manila.

France

Although comparatively few of the ancient foundations of France are still in existence, the republic does boast of the two oldest of them all, the Hotel Dieu in Lyons, and the Hotel Dieu in Paris. The former was established by Childebert about the year 542 A.D., and has been conducted as a hospital ever since. Most of the buildings are comparatively modern (1737 to 1842). Surely a history of almost fourteen hundred years devoted to the care of the sick may well furnish an inspiration for us in modern times.

The Hotel Dieu in Paris has almost as ancient a history, which has been well told by Mackay. It was established about 652 A.D., as an institution for the care of the ill among the poor. Very early it showed a tendency to division into departments, being one of the first to establish a separate obstetrical department, a " Service d'accouchement " in the women's annex. In 1300, it is recorded that the hospital had an attending staff of physicians and surgeons. The obstetrical department was conducted by the sages-femmes. At this time it had grown to a capacity of eight or nine hundred patients, and probably reached double that size in the fifteenth century. The number of beds was actually much less, as it was the practice to use enormous beds for four to six patients each. Included in the hospital equipment were two bath tubs on wheels.

The Hotel St. Louis in Paris was established by Henry IV in 1607 for plague victims; it now receives cases of diseases of the skin. In 1260, Louis IX founded the Hospital des Quinze Vingts as a home for the blind. Its name indicates a capacity of 300 inmates, and is an interesting survival of the vigesimal system of counting. It is still in operation near the Place de la Bastille; part of its endowment consists of the land on which the Folies-Bergères is situated.

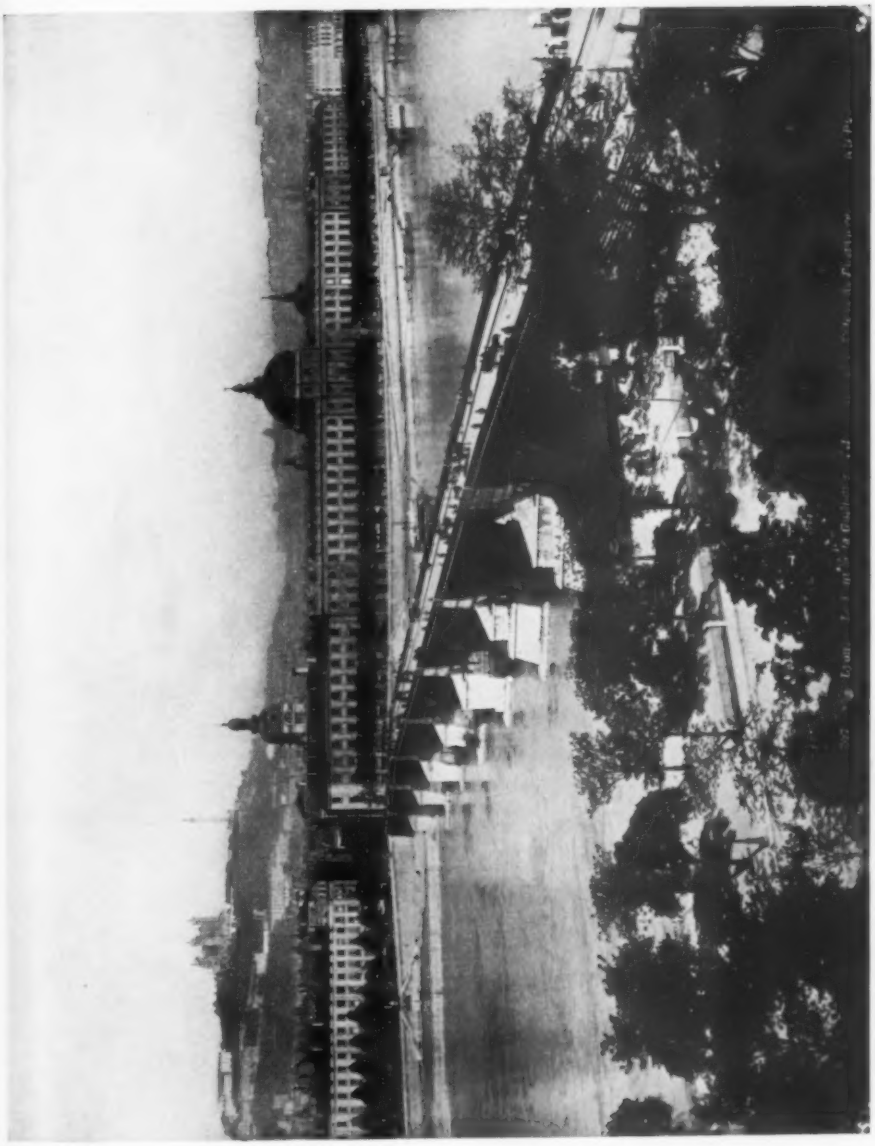

FIG. 1. Hotel Dieu, Lyons. Founded ca. 542 A.D. Buildings mostly 1737 to 1842. (N. D. Photo.)

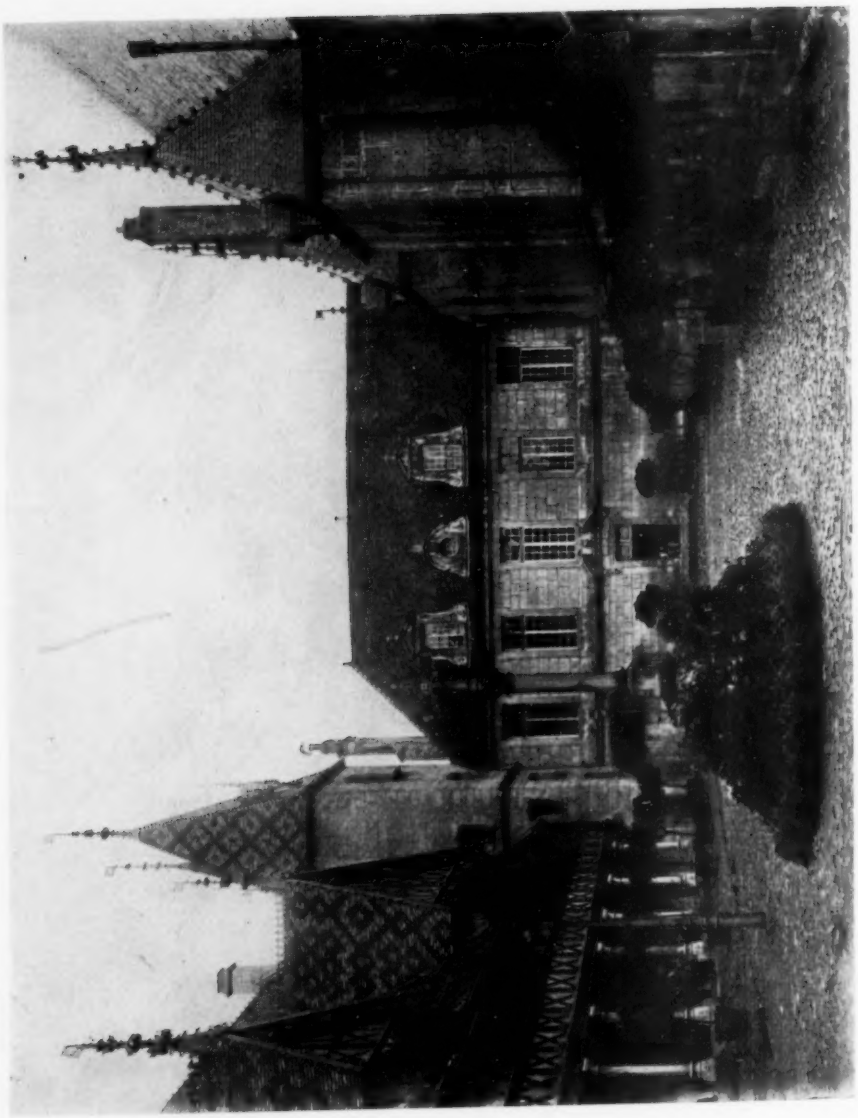

Fig. 2. L'Hotel Dieu, Beaune. Founded 1443, building occupied 1452. (Arch. du T. C. F.)

One of the most charming old hospitals in France is the Hotel Dieu in Beaune. This was founded in the year 1443, and it is the oldest hospital which has continuously occupied its original building. The first patient was admitted January 1, 1452. There are some interesting remains of former hospitals scattered elsewhere through France. Partly in ruins, the " Grande Salle of the Hotel Dieu " at Tonnere is frequently visited on account of its architectural beauty. It was established by Margaret of Burgundy about 1293. In Angers the archaeological museum is housed in the old Hospital St. Jean, which was originally given to the city by an early Count of Anjou, Henry II, King of England (1133 to 1189).

Holland and Belgium

There are several medieval hospitals in Amsterdam and Delft in Holland. In Belgium, the Hospital of St. John in Bruges was established in the twelfth century, though few traces of its early buildings remain. It is still conducted as an active up-to-date institution. In the former chapter room are housed some of Memling's finest work (1430 to 1494). The Hospice de la Poterie in Bruges is an asylum for elderly women, founded in 1276. Damme, formerly the port of Bruges, possesses an old institution, the Hospital of St. John, a home for old persons.

Italy

As the country in which Christianity first made its rapid spread, Italy boasts a number of early specimens. The oldest is the Santa Maria della Scala in Sienna, established in 898 A.D., with buildings dating largely from the fifteenth and sixteenth centuries. In Rome, the earliest was the Ospedale di Santo Spirito, founded in 1204 by Pope Innocent III, and shortly thereafter turned over by him to Guy de Montpellier as the first of the many conducted by the Order of the Holy Ghost. The buildings date from about fourteen hundred and later. Other old Roman institutions are the Ospedale della Consolazione, with parts dating from the thirteenth century, built on the site of an earlier hospital. The Ospedale di Santa Maria della Scala was established about the fourteenth century. These hospitals are still under the direction of the Order of the Holy Ghost. Other old hospitals in Rome are the Ospedale di San Giacomo, and the Ospedale di Giovanni. In Milan, the Ospedale Maggiore dates from 1456, and now serves as a city hospital. The City of Florence has many early survivals. Santa Mario Nuova was founded in 1287, by Falco Portinari (father of the supposed Beatrice of Dante); the buildings are largely seventeenth century. The Bonifazio (1377) has become an asylum for mental cases. San Giovanni di Dia was founded by Simone Vespucci about 1400.

One of the show places of Florence is the Ospedale de Santa Maria degli Innocenti, which was established as a foundlings hospital, and has served continuously as such up to the present time. The building was commenced

in 1421 after designs by Brunelleschi, and opened in 1444. Its history may be said to start much earlier, as there were combined with it the Hospitals of San Gallo (1218?), and Santa Maria della Scala (1316). For almost five hundred years, this institution has occupied its original building,

FIG. 3. Ospedale Degli Innocenti, Florence. Founded 1421, building occupied 1444. The medallions of della Robbia may be seen at the heads of the Columns.

although the interior arrangements have been modernized from time to time. It is a treasure house of early Italian art, possessing many specimens of Ghirlandaio, della Robbia, Brunelleschi, Poccetti, and others. Best known of these are the famous medallions of the infants in swaddling-bands, by della Robbia. There are fourteen of different designs at the head of the columns on the front facade.

The infants were formerly put in a small door opening at one end of the portico, but now most of them are received from an affiliated maternity hospital nearby. Complete supervision is continued until maturity. The institution has always been a favorite charity of the city, though in recent

times the income from its endowment has been augmented by contributions from the municipality. The records of the hospital are practically complete from the date of its foundation; the name of the first infant received is said to have been Agatha.

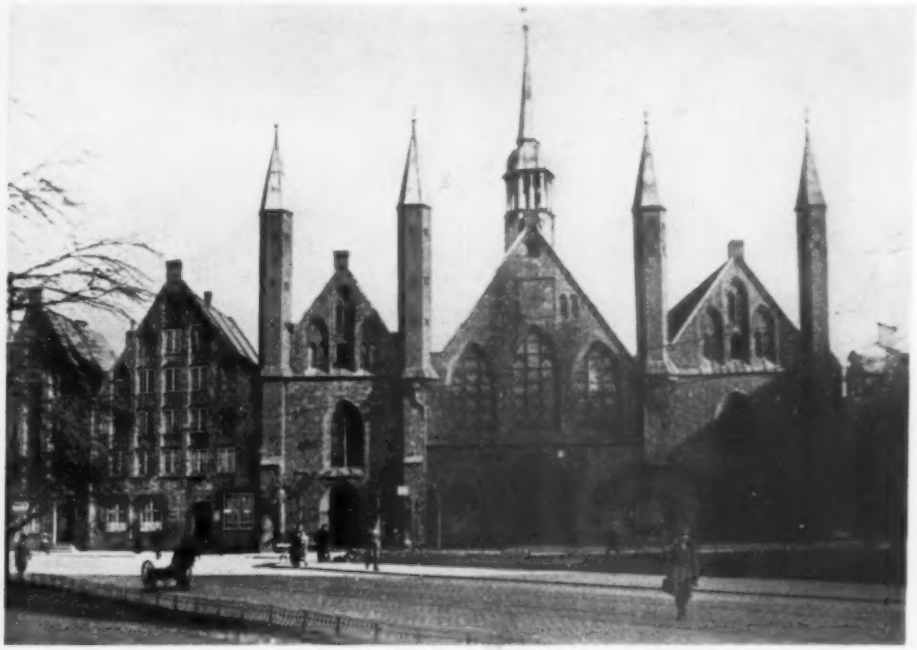

FIG. 4. Heiligen Geist Hospital, Luebeck. (Ger. Tour. Info. Office, N. Y.)

GERMANY

Hospital development in Germany took place largely in the thirteenth and fourteenth centuries through the activities of the Order of the Holy Ghost and the Order of the Lazarites. Virchow differentiates between the hospitals established within the city walls and those established without the city walls. The latter were usually leper houses. He lists a large number of these establishments, some in even the smallest villages in Germany. It is probable that their total number was over 2000 at one time.

The best preserved examples that the writer has seen are the ones at Luebeck and Rothenburg o.d. Tauber. In the former city, the Hospital of the Holy Ghost has always been an almshouse for elderly people. Originally established in 1240, it has occupied its present site since the 1400's, and retains a part of its early buildings. This institution illustrates one phase in hospital development which was more common in Germany than elsewhere, in that it was established by the municipality. The Hospital of the Holy Ghost in Rothenburg was originally built outside one of the gates, but when the city extended its ramparts it was included within the walls.

FIG. 5. Heiligen Geist Hospital, Rothenburg O. D. Tauber. Hospital to the right, city gate in the background.

FIG. 6. Heiligen Geist Hospital, Dinkelsbuehl. Hospital to the right, city gate in the background. (Ger. Tour. Info. Office, N. Y.)

This is an excellent specimen of the small city hospital, the major part of its support now being derived from city funds. The main building dates from the fifteenth century.

Another Holy Ghost Hospital is to be found in the picturesque town of Dinkelsbuehl. It comprises both a home for old people and a hospital, the latter housed in a new building erected in 1864. Additional examples of old hospitals still exist in Nuernberg, Wuerzburg, Luneberg, and in Bremen (St. Georgen Hospital, originally founded as a leper house). In Berlin, a Hospital of the Holy Ghost was built about 1278, but it has entirely disappeared, although there is an endowment remaining which is used for charitable purposes. St. Gertraudten Hospital was founded in the early 1400's " without the walls " on the square called " Spittelmarkt " at the east end of Leipzigerstrasse. It has recently been moved to a new location.

England

The first hospital recorded in England was built in York in Saxon times, 937 A.D. After the Conquest, many more were founded. They all suffered severely at the time of the Reformation, though a large number were preserved through the contributions of wealthy citizens. Those that had been founded as lay endowments continued their functions, for such philanthropy was a favorite form of charity by the well-to-do in the fifteenth and sixteenth centuries. Only the institutions in London were hospitals for the sick; those in the small communities were almost invariably of the almshouse type.

Of the hospitals, the most famous is St. Bartholomew's in London, which recently celebrated its 800th anniversary, having been established by Rahere in 1123. This one is well known to many physicians, as it is one of the great centers of medical teaching in the world. Its buildings date from 1760 and later. St. Thomas Hospital comes next in age (1215). St. Mary of Bethlehem was founded for the care of mental cases in 1247 (from its name was derived the word " bedlam ").

In numerous towns and villages of provincial England there will be found near the parish church a small building which is the almshouse. These institutions are of varied character as regards the nature of their endowments and the purpose for which they are now conducted. The original endowment usually was in the form of land, and naturally these endowments have been subjected to the vicissitudes of prosperity and depression for many centuries. Sometimes the institution owned the land outright, sometimes it was given a certain allowance from an estate. Certain of these almshouses were founded for the care of a number of old men, or old women, or for couples only. Charming examples are to be found in Canterbury, Sherborne, Burford, Norwich, Chipping Campden, Abington, Exeter, and in innumerable other communities.

Of this group the most perfect architectural specimen is the Hospital of

St. Cross at Winchester. It was established by Bishop Henri of Blois (a nephew of William the Conqueror) in 1123. It is housed in a double quadrangle of buildings which represent various gifts and additions from Norman times and later. Most of the quarters were built by Cardinal Beaufort in the sixteenth century. It is of the almshouse type providing a home

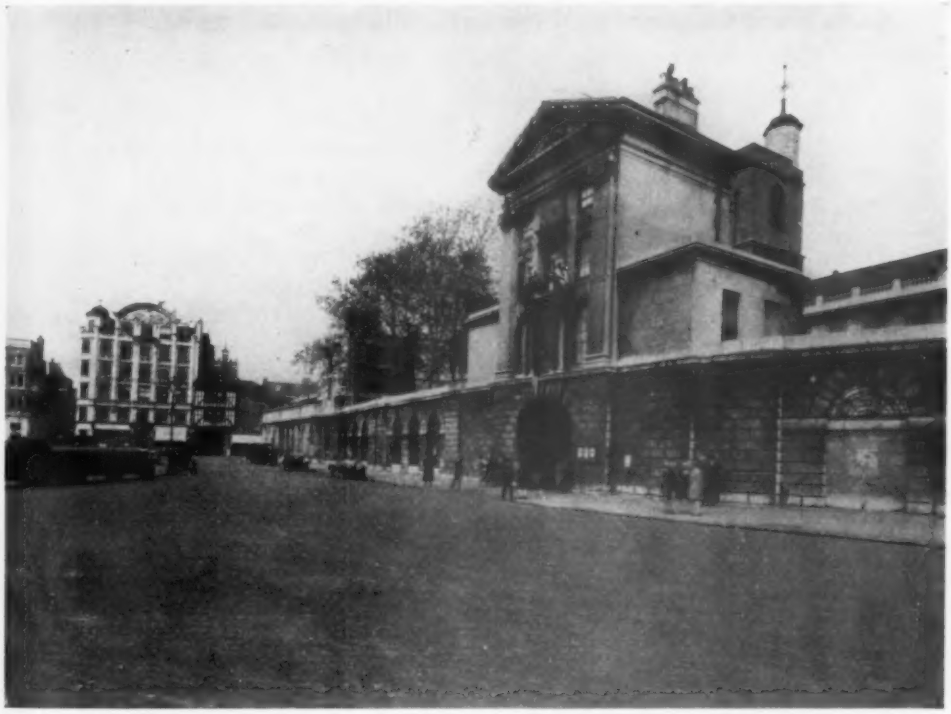

FIG. 7. St. Bartholomew's Hospital, London. Founded 1123 A.D. Buildings 1760 and later. (Photocrom Co. Ltd.)

for old men, and in addition (as a separate foundation) affords a home for 12 men of "gentle breeding." Its endowment also provides for the "wayfarer's dole," consisting of a pint of beer and some bread, which any wayfarer may have for the asking.

In other countries, there are a number of survivals. Of the many founded by the Arabians, there are several still in existence. The famous Bimaristan El Mansouri in Cairo, commonly called by the name of its founder, Qalaoun (1284), is now devoted exclusively to ophthalmological cases. A new addition to it was constructed about twenty years ago. One of the hospitals in Aleppo dates back to 1344 A.D.

In Spain, the Moors built a number of institutions during the time of their occupation (Cadiz, Seville, Toledo, etc.). The General Hospital in Madrid traces its foundation to three Moorish hospitals which were combined by Phillip II in 1566. There are a number of post-Moorish hospitals

and almshouses dating from the thirteenth to the sixteenth centuries in some of the other cities in Spain.

In this brief outline of the history of hospitals it has not been possible to discuss many of the interesting phases in their early development, nor to do more than make brief mention of a few of the hospitals which have been in existence for many centuries. Rich in historical and medical interest, as well as in architectural beauty, many of these institutions are well worth a visit by the physician traveling abroad.

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CASE REPORTS

AN UNUSUAL CASE OF OSTEOPSATHYROSIS (FRAGILITAS OSSIUM, LOBSTEIN'S DISEASE) *

By Everett B. Poole, M.D., *Greenville, South Carolina*

The disease which has been called fragilitas ossium, Lobstein's disease,[1] or osteopsathyrosis is characterized by the remarkable symptomatic triad of blue sclerae, brittle bones, and deafness. The general features of the disease have been well summarized by Apert,[2] and by Ottley,[3] who give comprehensive reviews of the literature. Ottley lists the following as characterizing the syndrome of osteopsathyrosis:

1. Fragility of bone.
2. Peculiar conformation and structure of bone.
3. Peculiar shape of the skull.
4. Laxity of the ligaments.
5. Blue coloration of the sclerae.
6. Deafness.
7. Abnormal electrical reaction of the muscles.
8. Miscellaneous abnormalities of the teeth, nails, and hair, and disturbances of the vasomotor system.
9. Familial character of the disease.

Brief comments on these peculiarities may help to delineate the clinical picture more clearly.

1. The bones fracture as the result of injuries so slight that they are often described as "spontaneous fractures." This is not due to a deficiency in calcium content, but is to be ascribed to morphological defects in the architecture of the bones.[4] The normal calcium-phosphorus ratio of the blood is not disturbed.

2. Changes, seen more distinctly in the long bones, comprise extreme slenderness, incurving of the shaft, most marked in its middle portion, thinning of the cortex and increased transparency to roentgen-rays. The epiphyses show no characteristic change.

3. The occipital prominence of the skull is exaggerated, and there is bulging of the temporal bones. The general effect is as if the entire skull had been subjected to powerful downward pressure on the vertex.

4. The ligaments show a remarkable degree of relaxation. As a consequence, pes planus, hyperextensibility of the fingers and knees, and frequent sprains and dislocations are observed.

5. Blue sclerae constitute a very striking feature of the syndrome, though by no means pathognomonic. They do occur in individuals who show no evidence of osteopsathyrosis. The blue color is not due to a deposit of pigment in the

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From The Department of Medicine, Duke University Hospital and School of Medicine.

sclerae but rather to scleral thinness and transparency which permit the choroidal pigment to be seen.

6. It is probable that the relaxation of the ligaments of the bones of the middle ear is responsible for the deafness so frequently reported,[2] though labyrinthine [5] and osteosclerotic [6] deafness have been described.

7. Upon electrical stimulation an incomplete reaction of degeneration is seen.

8. Thinness and fragility of the hair and translucency of the teeth ascribed to a deficiency in enamel have been noted. Subjects of the disease are said to be especially liable to migraine and vasomotor disturbances of various types.

9. The disease has repeatedly been observed in several generations. Apert concludes that the malady is inherited in the manner of a Mendelian dominant character. There is a wide variation in the distinctive features in individual cases which may display any or all of them. Deafness, fragility of bone, or any other feature may be inconspicuous or absent in any given case.[3] Blue sclerae may be the only apparent abnormality.[7] Francke [8] is of the opinion that the complete syndrome (blue sclerae, deafness, fragile bones) is found only in individuals whose parents have also shown it.

In the light of the foregoing brief description of osteopsathyrosis, the following case is reported.

Case Report

Luther C., a white male, aged 30; congenitally defective vision; blue sclerae; marked relaxation of ligaments producing pes planus and hypermobility of joints; blood chemistry normal; no fragility of bones.

The patient entered the hospital on February 7, 1934, complaining of pain in the head and eyes of two years' duration.

His father, mother and sister (the only sibling) were seen, and they state that no other member of the family has had any disease similar to that from which the patient is suffering. The parents state that the patient was not cyanotic at birth, nor could any evidence of rickets in childhood be obtained.

Since birth the patient's sight has been exceedingly poor, and he was almost completely blind in childhood with some improvement as he became older. He was also born with a marked deformity of the left chest wall. As long as he can remember he has noted very marked looseness of all the joints, especially those of the knees and ankles. He has always had flat feet. Two years ago the right cornea was severely injured by a foreign body, reducing the very poor vision of the eye to a bare perception of light. All useful vision remaining exists in the left eye, where he can see only the gross outlines of objects.

The patient presents a truly remarkable appearance (figure 1). He is very tall and thin with red hair and sharply contrasting indigo-blue sclerae. He looks older than his stated age of 30. The face is unusually long with a beak-like aquiline nose. The scapulae and acromial processes are very prominent, and there is marked anterior angulation of the left chest at the costo-chondral junction, producing a pigeon-breasted appearance.

The extremities are unusually long, the hands flattened, and, owing to a remarkable grade of ligamentous relaxation, the tarsal bones (figure 2) have moved downward to such an extent that they lie at a lower level than the rest of the foot, being covered by a mass of hyperkeratotic skin. The joints everywhere show an extreme degree of relaxation and hypermobility. This is especially marked in the fingers, shoulder joints and knees.

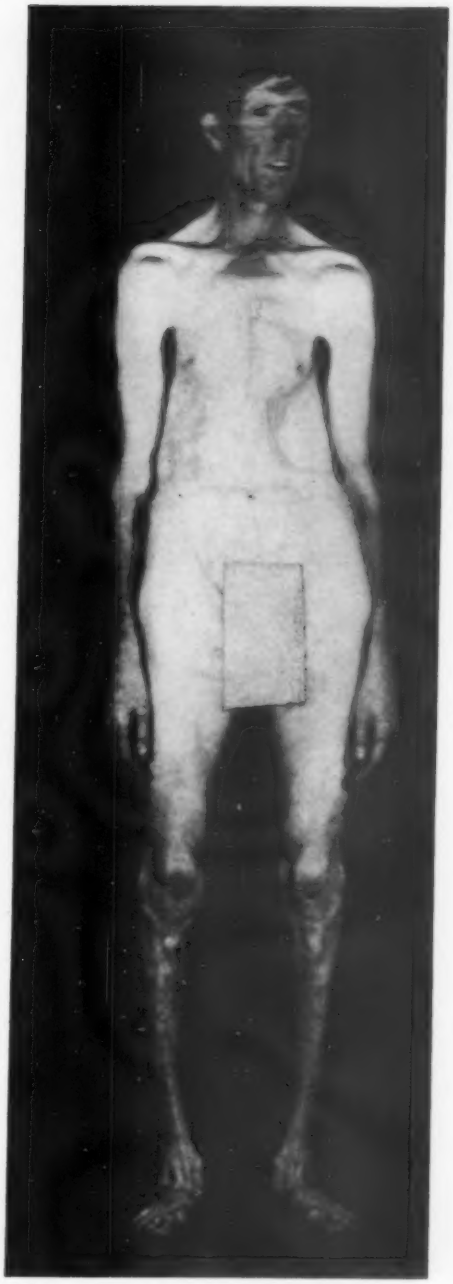

FIG. 1. General appearance of patient.

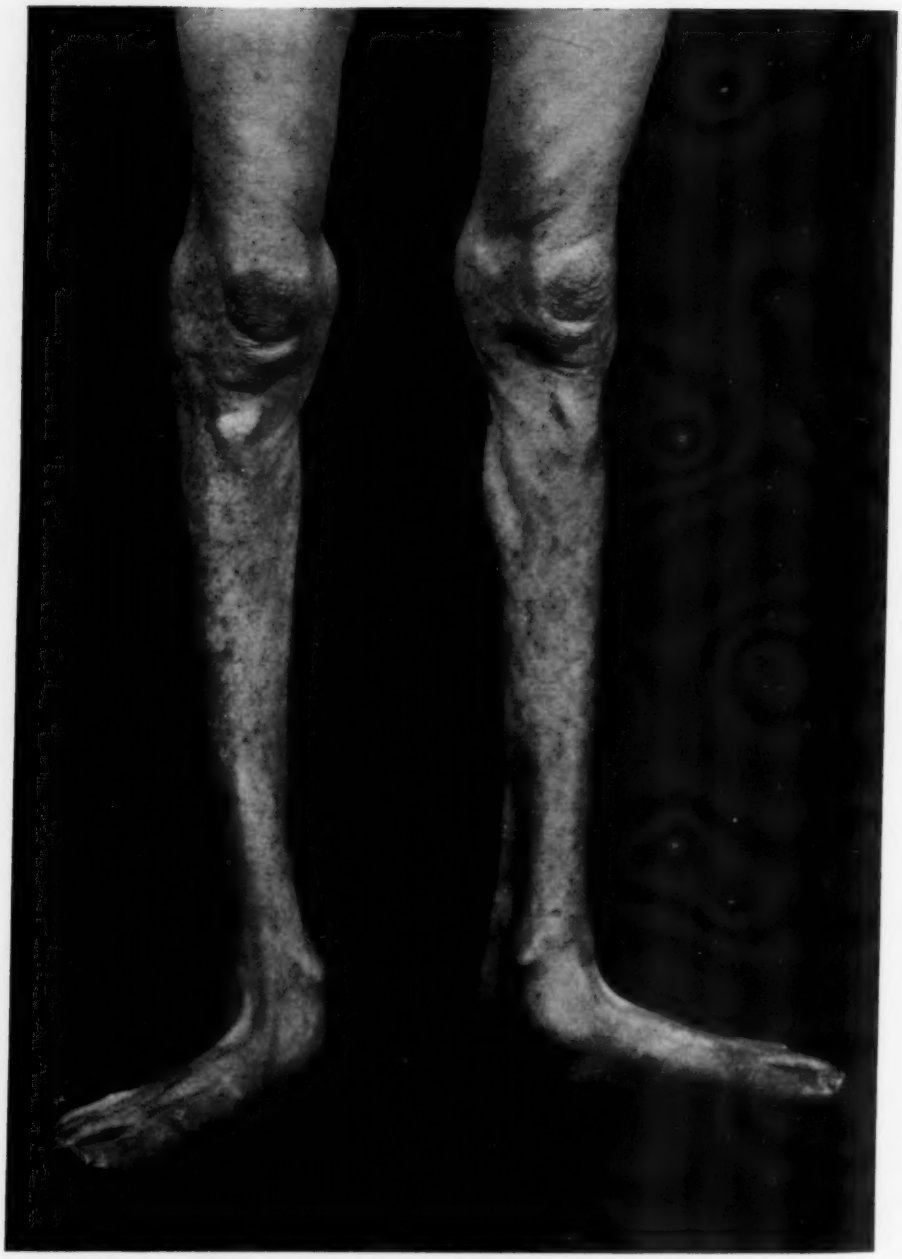

FIG. 2. Showing marked relaxation of the ligaments of the knees and feet.

The eyes show several noteworthy deviations from the normal (figure 3). The sclerae are really blue, not bluish. There are frequent nystagmoid jerks of the eyeballs, and it is then observed that the iris moves backward and forward in a wavy fashion as though having no anchorage from behind. No lens can be seen in either eye. The eyes show a definite divergent strabismus, and lateral movements cause nystagmoid jerkings. There is no evidence of injury to other cranial nerves except slight bilateral deafness by the audiometer test. Using air conduction, there was a loss of around 20 sensation units for both ears at all frequencies.

The lungs are negative, and the heart is not enlarged. There is a harsh systolic blow at the apex. The abdomen, genitalia and rectum show no abnormalities. The tendon reflexes in the upper extremities could not be obtained but are sluggish and equal in the lower extremities. Abdominals are present, Babinski bilaterally negative. No disturbance of sensation.

FIG. 3. Showing appearance of eyes. Partial iridectomy has been performed.

Very exhaustive accessory clinical examinations were made. Blood studies, gastric analyses, kidney examinations, sedimentation tests, stool examinations, spinal fluid studies, etc., all gave normal findings. Complete blood chemistry studies in the laboratory of Dr. W. A. Perlzweig revealed no noteworthy deviation from the normal. The serum calcium and phosphorus were within normal limits on three examinations.

Numerous roentgen-ray studies were made, but, except for the malformations noted above, nothing abnormal in the bones was found. There was no marked decalcification anywhere.

Biopsy sections from a ligament of the foot (cuneonavicular) were made, and although there appeared to be looseness of the collagenous fibers as compared to similar normal tissue prepared in the same way, findings were not sufficiently striking to justify serious consideration.

The condition of the eyes was diagnosed by Dr. Banks Anderson as ectopia lentis. Both eyes were operated upon and later on maximum correction established, but the end result was poor, vision with the best possible correction being 15/200 in the left and 10/200 in the right eye.

SUMMARY AND DISCUSSION

A case is presented showing three of the cardinal features of osteopsathyrosis (Lobstein's disease, fragilitas ossium), but with no history or other evidence of bone fracture. The blue sclerae, defective ligaments and slight deafness (together with the finding of ectopia lentis) can all be explained by a congenital defect in the structure of fibrous tissue forming the sclerae, ligaments and tendons.

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ORTHOSTATIC HYPOTENSION; REPORT OF A CASE*

By WANN LANGSTON, M.D., F.A.C.P.,
Oklahoma City, Oklahoma

IN 1926 Bradbury and Eggleston[1] reported three cases of a syndrome, the outstanding characteristics of which were "the occurrence of syncopal attacks after or during exertion or even after standing erect for some minutes. Other features in the three patients are a slow, unchanging pulse rate, incapacity to perspire, a lowered basal metabolism and signs of slight and indefinite changes in the nervous system. Each of these patients felt much worse during the heat of summer." Other symptoms were increased urinary output when patients were in recumbent position; youthful appearance; and loss of sexual desire and power. A slight increase in blood nitrogen and lessened phthalein output when patients were up and active were also noted.

The most outstanding characteristic in all these cases was the abrupt drop in blood pressure when the patient changed from a recumbent to a vertical position. This drop involved both the systolic and diastolic pressures, the extreme figures being a drop in case 1 from 105 systolic and 60 diastolic supine to 40 systolic and 28 diastolic standing; in case 2 from 158 systolic and 108 diastolic to 52 systolic and 40 diastolic, and in case 3 from 84 systolic and 60 diastolic to 45 systolic and 25 diastolic. It was noted that the pulse rate was relatively slow and remained approximately the same even when the blood pressure sank to critical levels.

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They designated this syndrome as "Postural Hypotension."

In 1928 Ghrist and Brown [2] reported two cases of this condition, Ashworth [3] two in 1929, Reicker and Upjohn [4] one in 1930, Barker and Coleman [5] one in 1931, and Sanders [6] one in 1931. In 1932 Laubry and Doumer [7] reported five cases, two of which have been questioned as not representing the characteristic syndrome,[8] and suggested the term "Orthostatic Hypotension" as being more descriptive than the one previously used. Barker [8] reported an additional case in 1933, Allen and Magee [9] one in 1934, Croll and Duthie [10] one, the first in Great Britain, in 1935, Weis [11] one in February 1935, and in July of this year Alvarez and Roth [12] reported the eighteenth case (if we exclude the two questionable cases of Laubry and Doumer), thus emphasizing the rarity of the condition or, what is more probable, the infrequency of its recognition.

The normal reactions of blood pressure and pulse rate to postural change have been studied by many investigators. In general, on changing from a horizontal to a vertical position there is slight elevation or depression in the systolic pressure, a definite rise of about 10 millimeters in the diastolic pressure, resulting in a lowered pulse pressure, and a definite increase in pulse rate amounting to 10 or more beats per minute.

Report of Case

History. C. W., a white male, school teacher, aged 56, was of Irish-Dutch extraction, of a family noted for longevity, the second of a family of nine children all of whom are living except two, an all-round college athlete (football, baseball, track and tennis) actively engaged in athletics up to the age of 45. He had always been healthy until the onset of the present condition except for minor ailments and except for a ligneous abscess behind the right ear at the age of 30 and an attack of iritis of the left eye at 39.

In August 1928, he was first troubled with frequent urination at night. Several doctors reported a few pus cells in the urine. He had several teeth extracted (one ulcerated) without relief. In October the urinary disturbance became more pronounced. In April 1934, he passed a large rough stone, preceded by passage of bloody mucous in urine. From 1928 to 1934 he drank artesian water of high mineral content. Prior to this time he had always perspired freely, but during this period it gradually ceased, and he perspired only from mid-chest up. Perspiration gradually ceased almost completely until the spring of this year when he perspired somewhat more freely. He did not note that he was particularly intolerant to hot weather.

In the fall of 1934 he noted a burning sensation across the abdomen, extending down to the feet and corresponding roughly to the area of anhidrosis. In January 1935, he had an attack of influenza, and after this the burning sensation mentioned above ceased and, as the weather became warmer, he began to perspire more freely.

About three years ago he began to note muscular weakness and fatigue about the hips. At first this was intermittent. He also noticed a similar weakness in the arms but much less marked, the symptom disappearing quickly with rest. About this time he began to "stoop" or "hump over" in walking, and his friends would tell him to "straighten up." A little later he would become very tired through the hips after walking a block or two, finding it necessary to rest after slight exertion. At the time he attributed this to the fact that he had sustained a fracture of the hip at football. Soon this localized fatigue became general all over the body and progressively worse, until now he experiences profound fatigue, giddiness and almost faints on changing from reclining to upright position, walking, and particularly on standing still for a few moments. Associated are fatigue and cramping in the muscles of the

legs, arms and neck. The muscles of the neck became so weak he could scarcely hold his head up, and this has become one of the most pronounced symptoms. The vocal cords would become fatigued and the voice husky and uncontrollable. The muscles of the arms seem too weak to lift any weight. These symptoms are most pronounced when he is standing, are relieved somewhat when he sits down, and he experiences prompt and almost complete relief when he lies down.

More recently he has experienced blurring of vision when standing or after exercise, promptly relieved by sitting down, bending forward or reclining.

He has noticed coldness of lower extremities below the knee for the past year, and since last winter he has noticed swelling of the feet and ankles. This has lately disappeared. There has been some numbness and tingling.

He passes very little urine during the day when he is up and around, but has nocturnal frequency and polyuria. Actual test after treatment was under way showed 12.5 ounces for the 14.5 waking hours, and 20 ounces for the 9.5 sleeping hours.

He has developed nervousness, a coarse tremor of the hands, and more or less mental sluggishness. He has also developed peculiar involuntary movements resembling laughter. This is more pronounced when he is weakest. He has also developed some emotionalism. There has been loss of sexual desire and potentia.

He came to me first on August 2, 1935, with this story and the diagnosis of heart trouble and low blood pressure.

Examination, August 2, 1935. A well developed and well nourished middle-aged white man, apparently not as old as stated age. Temperature 99.2° F., pulse 84, blood pressure reclining 120 systolic and 80 diastolic. There is no apparent anemia, cyanosis, jaundice, edema, dyspnea or distress. The face is rather florid, the beard somewhat thinner than in the average man, the hair graying, and a tendency to baldness. The eyes, ears, nose, mouth, teeth, tongue and pharynx show no significant changes. The thyroid is not enlarged and there is no cervical adenopathy.

Heart shows slight enlargement to the left. There are no murmurs or abnormal accentuations. The heart tones are normal. Lungs: No abnormal findings. Chest wall: No abnormality. Abdomen: No abnormality noted. The liver and spleen are not palpable. No areas of tenderness, and no masses to be felt. Genitalia: No abnormality found. Rectal: Negative findings. Neuro-muscular system: The musculature is apparently normal. There is a definite coarse tremor of the fingers, more marked in the left hand. Tendon and superficial reflexes normal. Pupillary reactions are also normal. Integument: The skin is soft and pliable. There are no evidences of pigmentation. There is no obvious perspiration.

Blood: hemoglobin 90 per cent Sahli; red blood cells 4,510,000; white blood cells 6,100; N. 67 per cent, L. 33 per cent. Sugar tolerance after 100 grams of glucose: 80–150–125 mg. Wassermann and Kahn negative. N.P.N., 51.0 mg. Urea N. 26.7 mg. Phthalein output reduced, although he collapsed and voided involuntarily 20 minutes after intravenous administration of the dye. For the balance of the two hours the elimination was 25 per cent.

As stated above, the blood pressure at the first examination was 120 systolic and 80 diastolic with patient in recumbent position. Upon sitting up an immediate drop to 95 systolic and 70 diastolic was noted. The following day I rechecked the blood pressure and found the following: recumbent, 125 systolic and 80 diastolic; sitting, 90 systolic and 60 diastolic; standing, 60 systolic and ? diastolic, with weakness and syncope. During these observations the pulse rate was around 80, and varied scarcely at all from this figure, even when pressure went to extreme low levels. I have made many blood pressure observations always with the same general results, namely, a marked drop in both systolic and diastolic pressures upon changing from horizontal to vertical positions, with little or no change in the pulse rate. Typical are the observations made on August 28, 1935, and checked with Dr. W. F. Keller. (Figure 1.)

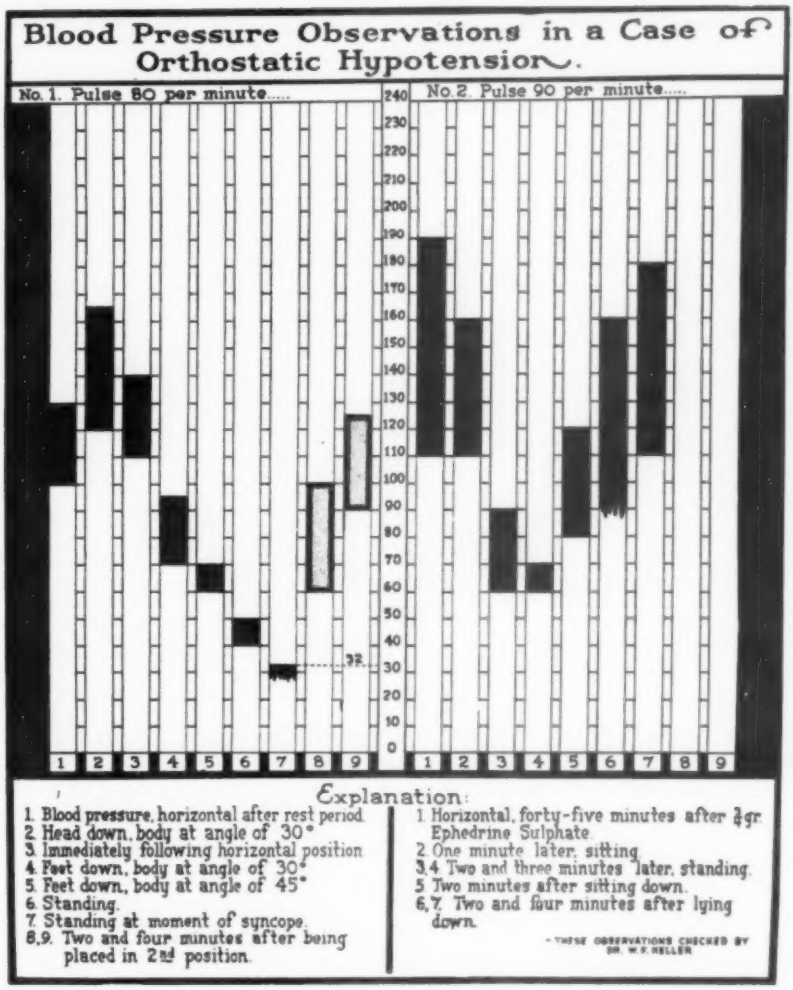

FIG. 1.

The following observation, noted on different occasions, to me is unique and perhaps important: During attacks of great weakness the patient has involuntary paroxysms exactly simulating laughter, during which he chuckles and manifests the typical contractions of the abdominal muscles, but he feels no desire to laugh and the facies indicates no emotion of amusement. When a normal individual laughs the blood pressure is raised; when this man has such a paroxysm his pressure is raised. Ghrist and Brown in one of their cases noted what may be an analogous phenomenon, namely, clonic convulsions just preceding syncope, explained by the patient as being voluntary muscular contractions in an effort to stand.

To summarize the case: An apparently healthy middle-aged man presents certain definite subjective and objective findings, namely, orthostatic drop in both systolic and diastolic pressures without compensatory increase in pulse rate;

orthostatic weakness, giddiness and syncope; orthostatic oliguria; increase in blood urea nitrogen, with reduced phthalein output; hypohidrosis with geographic distribution; loss of libido and potentia; nervousness, tremor, and involuntary convulsive paroxysms resembling laughter when very weak—all of the characteristic findings of the syndrome designated as orthostatic hypotension.

An analysis of the cases thus far reported is shown in the following table. This reveals orthostatic hypotension and orthostatic weakness, giddiness and

SIGNIFICANT FINDINGS IN CASES REPORTED

Symptoms

Symptom	Positive	Negative	Doubtful	This case
Orthostatic severe syncope	11	7	0	+
Orthostatic weakness or mild syncope	17	1	0	+
Orthostatic oliguria	10	0	8	+
Anhidrosis or hypohidrosis	10	3	5	+
Intolerance to hot weather	4	2	12	0
Loss of libido and potentia	3	5	10	+

Physical and Laboratory Findings

Finding	Positive	Negative	Doubtful	This case
Orthostatic hypotension	18	0	0	+
Slow or unchanging pulse rate with changing position	12	4	2	+
Lowered metabolic rate	10	2	6	?
Increased blood urea nitrogen	7	0	11	+
Youthful appearance	4	7	7	+
Slight anemia	5	6	7	0

syncope as invariable phenomena, and lack of compensatory tachycardia, lowered metabolic rate, nitrogen retention, and orthostatic oliguria, as almost invariable.

In addition to the above practically constant findings, others of greater or less significance are changes in the pupillary reactions, and other neurological changes, insomnia, weight loss, dyspnea, geographic anhidrosis, etc.

Bradbury and Eggleston found that the administration of epinephrine was followed by an increase in systolic and pulse pressures and in pulse rate, but that the diastolic pressure was not materially affected. They concluded that epinephrine did not cause vaso-constriction in these cases. Atropine caused dryness of the mouth and flushing of the skin in two cases, but no increase in

pulse rate. Pilocarpine caused salivation and sweating in two cases. In general, these observations have been confirmed by other investigators. Bradbury and Eggleston conclude that "paralysis of the sympathetic vaso-constrictor endings seems to be the only adequate explanation of the blood pressure reactions in these three cases. It accounts for the absence of vaso-constriction following the injection of epinephrine, and it explains the total absence of the normal vasomotor control by which blood pressure is maintained at a nearly constant level in the face of changes in the position of the body in normal persons." In general, these conclusions have been concurred in by subsequent authors. Ghrist and Brown thought that "the essential disturbance in this disease is lack of resistance in the splanchnic vessels to shifts in the blood mass and absent or diminished vagus regulation of the heart rate to changes in blood pressure. The opinion is advanced that this disease represents a hypotonic state of the myoneural structures of the sympathetic and parasympathetic nervous system of unknown origin." Barker explains these phenomena "by loss of reflex posture or orthostatic vaso-constriction necessary to maintain normal blood pressure against the force of gravity . . . and by loss of reflex acceleration of the cardiac rate." He attributes the accelerator effect of epinephrine and ephedrine in these cases to their direct effect on the heart muscle. Alvarez and Roth believe the essential pathological physiology is in the "sympathetic control of the caliber of the vessels in the abdomen."

Prof. J. A. MacWilliam, who studied the case of Croll and Duthie, found that in normal individuals "the slower heart rate in the horizontal posture, as compared with the sitting, is essentially due to the action of the carotid sinus reflex, while the quicker rate in standing than in sitting is mediated through afferent impulses from the lower limbs which are also concerned in the maintenance of the compensatory adjustments (vaso-constriction in the splanchnic area and elsewhere) involved in keeping up the aortic pressure in the erect posture." He believes that "both pulse rate and blood pressure adjustments in the standing posture are influenced by afferent impulses from the lower limbs, apparently originating in some part of the vascular circuit in these limbs," and that in these cases there is a disturbance of this mechanism, an opinion that seems to be refuted by Alvarez who points out that while orthostatic hypotension is not produced by lumbar sympathectomy, it is produced for a time by anterior rhizotomy.

Alvarez and Roth also found that epinephrine intravenously did not cause peripheral vaso-constriction, although it did cause elevation of pulse rate and systolic blood pressure. The fact that atropine does not cause increase in pulse rate in these cases suggests interference with the normal sympathetic accelerator mechanism of the heart. On the other hand the sympathetic supply to the sweat glands is intact if depressed since the reaction to pilocarpine is present to an extent at least.

The effects of various therapeutic agents have been observed. Epinephrine, in addition to raising the systolic pressure and pulse rate, gave temporary symptomatic relief. Thyroxine gave questionable relief in the work of Bradbury and Eggleston. The use of a tight abdominal binder has given variable results in different patients. Ghrist and Brown first noted the beneficial effects of ephedrine. Barker, and later Allen and White noted improvement from ergotamine tartrate, but the disagreeable symptoms seemed to more than counterbalance the

benefits. Various other remedies have been tried, but to date ephedrine sulphate seems to have given most consistent and lasting improvement subjectively and objectively.

Having noted the beneficial effects of suprarenal cortical hormone (eschatin) in a case of Addison's disease with orthostatic hypotension (secondary), I decided to try this remedy with my patient, and accordingly, on August 3, I gave him 1 c.c. intramuscularly, and he reported that within an hour or two he felt stronger. I repeated this on August 4, omitted it on the fifth, and on the morning of the sixth he collapsed in the elevator on his way to my office. I gave him 5 c.c. of eschatin immediately, and within 30 minutes the blood pressure was 150 systolic and 100 diastolic, with patient recumbent. The following day he was feeling better, the blood pressure being 160 systolic and 100 diastolic reclining and 120 systolic and 80 diastolic sitting, in the forenoon, and in the afternoon, after some walking during the interval, 125 systolic and 90 diastolic sitting. I did not repeat the eschatin on this date.

On the morning of August 8 he took 3/8 gr. ephedrine sulphate and reported to the office at 9:00 o'clock. At this time his pressure was 120 systolic and 80 diastolic reclining, and 90 systolic and 60 diastolic sitting. I gave 0.25 c.c. eschatin and in 20 minutes the reading was 150 systolic and 100 diastolic, reclining. On the ninth he received 0.25 c.c. and on the tenth when he reported the pressure was 90 systolic and 60 diastolic, and he complained of weakness. I gave him 0.5 c.c. with only slight improvement. From August 10 to August 21 he took 1/3 c.c. eschatin and 3/4 gr. ephedrine sulphate daily, and though his condition was better than before he began treatment, it was far from being satisfactory. He noted that the ephedrine invariably caused increased pulse rate, heart consciousness and nervousness. He reported on the twenty-first, with the following blood pressure: 125 systolic and 80 diastolic, reclining, 90 systolic and 60 diastolic, sitting. At 3:00 o'clock p.m. it was 100 systolic and 70 diastolic and 60 systolic and 40 diastolic. I gave him 0.5 c.c. eschatin and in 30 minutes the pressure was 140 systolic and 90 diastolic, and 100 systolic and 60 diastolic sitting. From the twenty-first to the twenty-seventh, ephedrine was omitted and 0.5 c.c. eschatin twice daily was administered. He was fairly comfortable during this period but experienced considerable weakness. He reported on August 28 when the series of observations charted was made.

From August 28 to September 3 he took ephedrine and amytal three times a day, but the cumulative effect of the amytal was too disturbing. I then outlined a course of procedure whereby he took one-half grain of ephedrine before getting up in the morning and one-fourth grain every four hours during the day. He felt, however, that the larger dose in the morning was unnecessary, he has settled down to three or four one-quarter grain doses daily, and his condition has been much more satisfactory.

Although Weis has reported a case as cured by this therapy, and his observations over a considerable period of time seem to substantiate it, it seems too much to expect a cure in this case, although one hopes to make life livable for him.

Weakness, dizziness, faintness, a tendency to syncope, on suddenly changing from a reclining to an upright posture or upon standing still for a few moments, are not uncommon complaints. If every such case were carefully considered and blood pressure readings made in both positions, it is entirely possible that many other cases might be recognized. In view of the frequency of anhidrosis or hypohidrosis in these cases, all patients complaining of this symptom should be investigated with this entity in mind.

One occasionally sees individuals, usually of a definite ptotic type with low blood pressure, who have been improved apparently by the use of a tight abdominal binder. Improvement is not due to replacement of the abdominal viscera, for some of us have demonstrated with the fluoroscope that this does not occur in spite of the symptomatic improvement. A study of this case and of the reports of others leads one to believe that any such benefits come from forcing the blood out of the splanchnic area, and that in all probability in some of the cases at least the symptoms are due to splanchnic vascular atonicity.

Certain acute processes, notably influenza, affect blood pressure. Is it not probable that some of the profound debility in influenza may be on the same basis?

Summary

1. There appears to be a definite entity with characteristic findings which may be properly designated as orthostatic hypotension.

2. The chief characteristics are orthostatic hypotension, orthostatic weakness or syncope, absence of compensatory tachycardia on rising from reclining to upright position, orthostatic oliguria with nitrogen retention and decreased phthalein output.

3. The syndrome seems to be on a basis of sympathetic nerve ending impairment.

4. The literature has been reviewed briefly.

5. Eighteen cases have been reported previously and another is presented here.

6. To date ephedrine sulphate has given most consistent benefit.

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COMPLETE HEART BLOCK FROM SCLEROSIS OF THE BUNDLE OF HIS *

By Ben R. Heninger, M.D., F.A.C.P., and K. L. Dickens, M.S., M.B.,
New Orleans, Louisiana

Complete heart block may result from various types of lesions involving the bundle of His or other parts of the conduction system. Most of the cases of complete heart block reported in the literature were the result of syphilitic gummas. There are on record isolated cases of heart block in which fatty infiltrations have caused auricular-ventricular dissociation; in others, tumors, such as endotheliomas and sarcomas, have been found to destroy the conduction pathways of the bundle. On the other hand, there are numerous cases in which there was clinical heart block, but at autopsy no lesion was found in the bundle of His.

In a recent paper, Yater and Cornell supply evidence which indicates that heart block may be due to calcareous lesions involving the bundle of His, as well as the subendothelial surface of the heart. Yater further states that this specific form of lesion producing complete heart block must be rare, as he could find only 47 cases which have been sufficiently studied and in which the criteria fulfilled the requirements for this diagnosis. It is possible that this condition may be much more frequent than the literature leads one to believe. On account of the rarity of complete heart block due to calcareous disease of the bundle of His, we present this report with the hope that it may stimulate a search for similar cases.

Case Report

Case History. An unemployed Italian male, aged 62, was admitted to Touro Infirmary, on the service of Dr. Emile Block, June 3, 1934 and died June 9, 1934. The patient was referred to one of us (B. R. H.) within 20 hours after admission, with a history that his present illness started three weeks previously. Predominating symptoms were marked dyspnea, swelling of the ankles, and inability to sleep at night. All symptoms were progressive in character until the occurrence of abdominal swelling, which had been present for one week. During this period there was precordial pain, running down the arms; later there was a productive cough.

Physical Examination. Examination revealed a well-developed male, of large frame, with moderate cyanosis and generalized edema. Dyspnea was unusually marked. The heart was markedly enlarged to the left. The apex impulse was easily seen and felt at the anterior axillary line on the left side. The right border extended outward about 5 cm. from the median line in the third interspace. The cardiohepatic angle could not be made out; the impression was gained that there was a pericardial effusion, although the classical signs were absent. The heart sounds were feeble, especially at the apex, while at the base they were more easily audible. The pulse and heart rate, while the patient was lying down, was 30 per minute. The peripheral vessels were moderately sclerosed. The blood pressure was equal on both sides, being 215 systolic and 110 diastolic. The lungs showed fine crepitations at both bases. The liver was markedly enlarged downward and very tender. There was free fluid in the abdomen as shown by shifting dullness.

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From the Departments of Medicine and Anatomy, Louisiana State University Medical Center, New Orleans, La.

Our impression of the case was arteriosclerotic type of heart disease with hypertension, congestive heart failure, complete heart block, and general anasarca.

An electrocardiogram taken shortly after entrance into the hospital (figure 1) revealed heart block of high grade, with infrequent ventricular extrasystoles. A

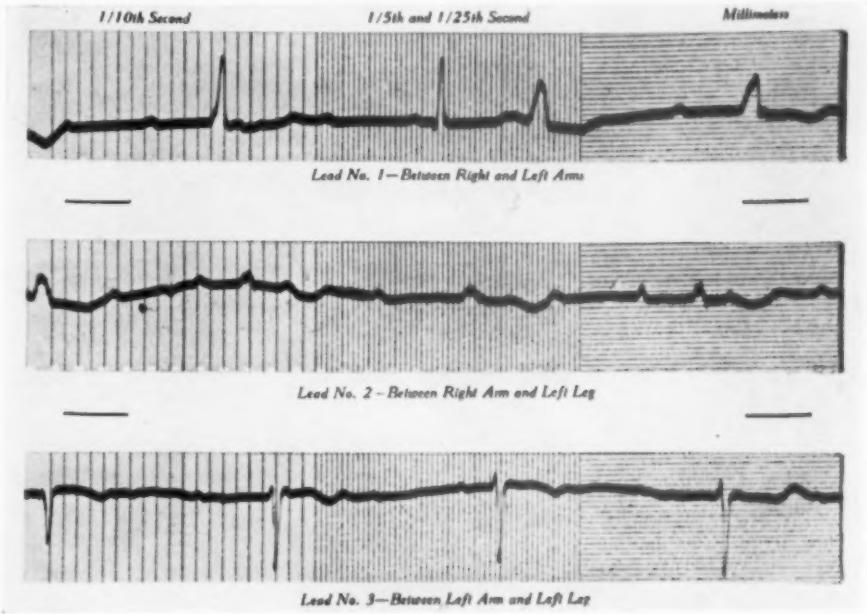
1/10th Second
1/5th and 1/25th Second
Millimeters
Lead No. 1—Between Right and Left Arms
Lead No. 2—Between Right Arm and Left Leg
Lead No. 3—Between Left Arm and Left Leg

FIG. 1.

second cardiogram taken 6/5/34 revealed about the same picture; the ventricular rate in both was 30 to 45 per minute.

Progress Notes. The patient was placed on the conventional treatment for congestive heart failure, including limitation of fluids, a salt-poor diet, and digalein, 2 cat units every four hours for a period of three days, totaling 24 cat units. Following this digitalization, there seemed to be definite improvement; the area of cardiac dullness apparently diminished, there was less orthopnea, and the mental attitude of the patient was very noticeably improved. Following the discontinuance of digitalis the apparent improvement was maintained for about 30 hours, but then the dyspnea returned in even more marked degree. With this, the patient seemed to develop mental disturbances, in that he was unwilling to remain in the hospital. Finally, smothering spells became so distressing that the patient could hardly be kept in bed. Morphine with atropine was given hypodermically without much benefit. Suddenly, while the patient was sitting up in bed, he developed convulsive seizures. The pulse varied from 28 to nearly 50 per minute. Barium chloride, gr. i every three hours, was given for the next 24 hours, but in spite of this, repeated convulsions ensued, lasting for variable periods of time. The patient died suddenly on the morning of June 9, 1934.

Pathological Examination: Gross Examination of the Heart and Pericardium. The pericardium was smooth and glistening. There were approximately 75 c.c. of clear amber-colored fluid in the pericardial sac. The heart weighed 460 grams and showed hypertrophy of the left ventricle. There was a moderate amount of fatty infiltration evident beneath the epicardial surface. The organ was removed and

sectioned. The myocardium was reddish-brown in color and measured 3 cm. in thickness. Scattered throughout it were areas of degeneration. The endocardium was pinkish-gray in color, smooth and glistening in appearance. The foramen ovale was closed. All valves were competent. The ostia of the coronary arteries were patent; however, upon tracing the arteries they were markedly sclerotic. The in-

FIG. 2. View of left ventricle and aorta. Calcium mass (*C*) shown diagrammatically in approximate position after blocks in area, *B*, have been taken out. Area *S* indicates where a further section was removed for study of the muscular septum. Arrow points to the right coronary artery orifice.

timal surface of the aorta was pinkish-yellow in color, with many arteriosclerotic plaques scattered throughout.

Histopathologic Examination of the Heart. Two blocks of tissue were removed from the heart at the junction of the membranous and muscular septum. These blocks were taken so as to include an area from the bases of the right and left anterior aortic valves to within about 1 cm. of the muscular septum of the heart. Microscopic sections were taken at various intervals so as to determine the length and distribution of the fibro-calcareous mass, A–V bundle and its branches. Figure 2 shows the opened left ventricle and aorta with area from which the blocks for examination were taken. An additional section was taken from the muscular septum for study of the A–V bundle and its branches. The arrow points to the right coronary artery, thus giving exact anatomical location of the blocks. The approximate location of the calcareous mass is indicated diagrammatically.

The tissues were partially decalcified and sections cut at 10 micra. The sections were stained with hematoxylin and eosin and with Mallory's connective tissue stain. Sections were taken from various regions and approximate length of the mass was ascertained. Figure 3 reveals the position of the mass and its characteristic nature. Figure 4 is a higher magnification of a portion of figure 3.

FIG. 3. Low magnification of membranous and muscular septum revealing the exact position of the calcium mass. *RA* is right auricle, *A–V* indicates the atrio-ventricular bundle; *C* indicates the two calcium masses with small particles of the homogeneous substance scattered between. An edge of the aortic cusp is shown above. *S* indicates the muscular portion of the septum. (45 × mag.)

A calcareous mass was revealed at the junction of the membranous and muscular septum in the myocardial portion, which was surrounded by dense fibrous connective tissue. Near the center of the mass this fibrous connective tissue separated the cal-

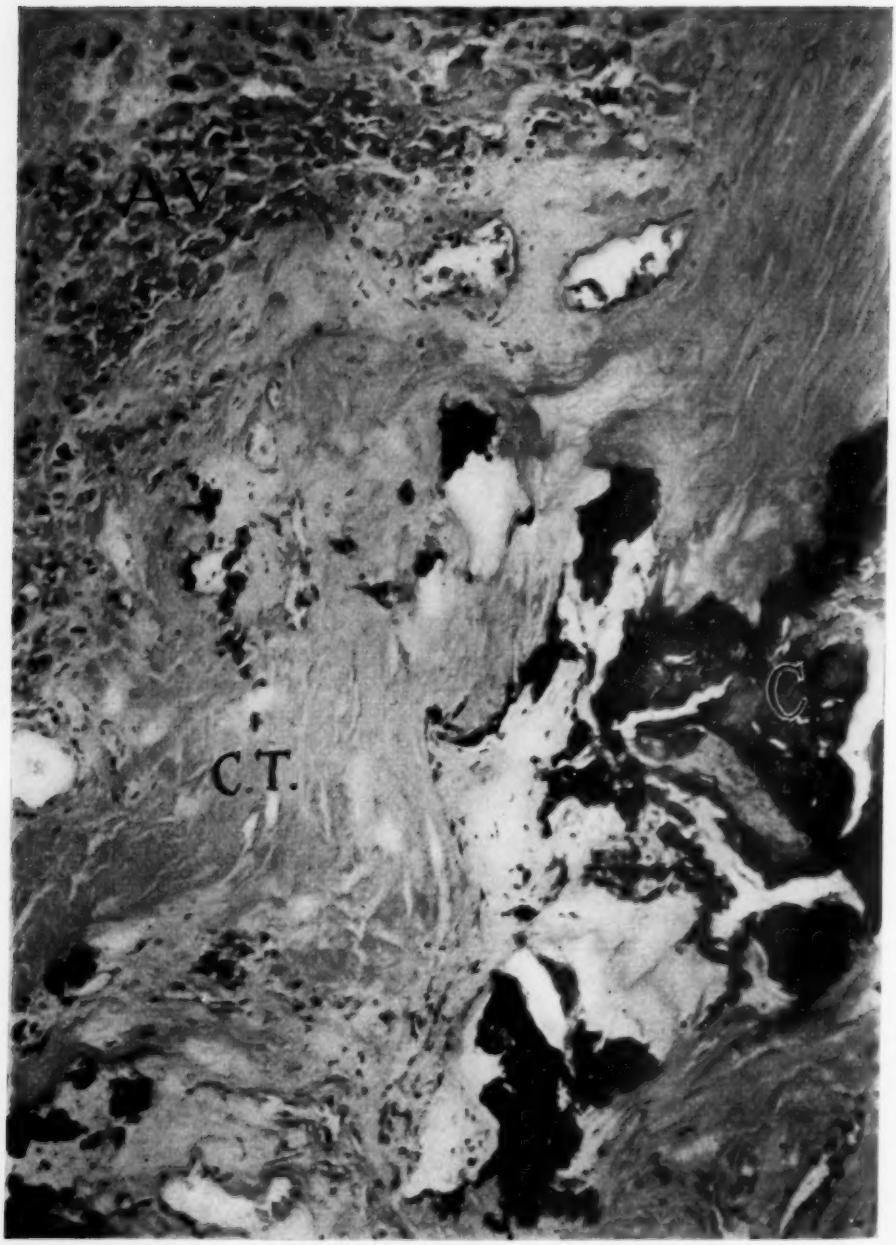

FIG. 4. Reveals a higher magnification of portion of mass and A–V bundle as shown in figure 3. *C* indicates the calcium mass surrounded by dense fibrous connective tissue, *CT*, AV bundle (*A–V*) is seen being impinged upon and invaded by the fibro-calcareous mass. (100 × mag.)

careous mass into two parts. Each mass measured approximately 1.5 mm. in diameter and 6 mm. in length. Near the ends of the mass it became smaller and narrower and finally disappeared. The mass ran parallel to the base of the aortic leaflet of the mitral valve (figure 2). The mass was largely on the left side of the septum, it impinged upon the A–V bundle near the center and at some places was seen to invade the bundle substance. Small portions of calcified material were seen scattered around the main mass. The A–V bundle and its branches were apparently normal in cellular structure throughout. There were a few lymphocytes in and around the mass.

The muscular septum was quite hypertrophied, as were the individual muscle cells. There were no endothelial changes of note, and conduction system was apparently normal in cellular structure. The aortic valves showed evidences of slight calcification in their bases, but were otherwise competent. A number of small arteries around the calcified mass showed definite sclerotic changes, but none were completely obliterated. The coronary arteries were definitely sclerosed. The photograph of the heart and photomicrographs further add to this description.

We wish to express our appreciation to Dr. John S. Lanford, Director of the Department of Pathology, Touro Infirmary, New Orleans, who performed the autopsy.

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EDITORIAL

CUSHING'S SYNDROME AND TUMORS OF THE ADRENAL CORTEX

In 1932, Cushing [1] published an account of the syndrome which now goes by his name and which he called pituitary basophilism. As is well known, he was able to collect a group of cases associated with basophilic tumors of the hypophysis, all of which showed some or many of the following characteristics: adiposity of the face, neck, and trunk, the extremities not being affected; vascular hypertension; hirsuties, particularly of the face and trunk in females; impotence or amenorrhea; cyanosis and edema of the extremities; a tendency to polycythemia, with a florid or plethoric complexion; dryness of the skin, often with acne, and particularly with purplish linae atrophicae; osteoporosis; glycosuria or albuminuria; and variable backache, weakness, and fatigability. Other cases were soon reported, but it became evident that such a syndrome might also occur in the absence of a pituitary tumor, associated with other endocrine lesions particularly of the suprarenal cortex and thymus.[2, 3] Pituitary basophilism, therefore, or a syndrome which cannot be distinguished from it, although frequently accompanied by a pituitary growth, is not invariably so related. Examination of a large number of pituitary glands by Costello,[4] with serial sections, in cases where no endocrine disturbance was obvious clinically, also indicated that such tumors were to be found in the absence of the symptoms which have been described.

Studies recently reported by Crooke [5] may have fundamental importance in throwing light upon this problem. He has discovered that a hyaline change is present in the basophilic elements of the anterior pituitary, often with cellular distortion, and with a diminution in the number of basophilic granules present, in cases of pituitary basophilism. The lesion is not found in the basophilic adenomata when present, but only in the proper glandular tissue. This change was found not only in cases of Cushing's syndrome with basophilic adenoma of the pituitary, but also in similar clinical disorders in which neoplasms of the thymus, or growths or hyperplasia of the adrenal cortex, were the conspicuous lesion, and in which a basophilic pituitary

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adenoma was not found after most careful search. All of these cases suffered from hypertension, as did those described by Cushing. Crooke believes this hyaline change in the basophiles is an expression of altered physiological activity rather than a degenerative change in the ordinary sense. He has also made interesting observations on the pituitary in Addison's disease, where extreme reduction in the number of basophiles and the presence of abnormal basophilic transitional cells are to be found. Nicholson [6] has reported recently a difference in the histologic picture in pituitary glands from patients with Addison's disease due to cortical atrophy and those due to tuberculosis. Only in the first group was he able to show reduction in the number of basophiles and the appearance of abnormal basophilic cells. Crooke suggests that this reduction in these elements is associated with the cause of the hypotension and perhaps of the hypoglycemia which are found. Since cortical hormone therapy in Addison's disease does not seem to influence this pituitary lesion, a plausible reason is afforded for the slight effect which it also has on the clinical course of the hypotension.

Other relationships of the adrenal cortex are indicated, however, by certain cases of cortical tumor which, instead of being associated with Cushing's syndrome, exhibit the even more striking clinical phenomena of stimulation or reversal of sex. In this they seem to show a sharp difference from the first named condition, in which the characteristic sex changes are those of inhibition or depression, rather than of virilism. There is, however, considerable uncertainty as to just how clear a distinction may be drawn between the two conditions. If a hormonal principle, elaborated by the tumor cells, is responsible for the sex changes, as seems altogether likely, it would appear to be more closely related to the gonads than to the pituitary. Removal of the tumor, in a number of brilliant instances, has resulted in practical cure of the patient, with disappearance of the abnormal sex phenomena.[7] It seems probable that the salt and water hormone of the adrenal cortex, which is to a certain degree effective in Addison's disease, has nothing to do with this sex reversal or sex stimulation, at least not in any clear and direct way. This is, of course, remarkable, since the methods of extracting this material, by means of lipid solvents, are precisely those which have been found so effective in the isolation of the gonadal hormones. Hartman has, indeed, reported a separate lactogenic principle from the adrenal cortex.[8] The evidence available, therefore does seem to suggest that more than one hormonal principle may be present in the adrenal cortex.

The closely related embryological origin of adrenal cortex and gonads, within the genital ridge, and the occurrence of the "X" layer between reticularis and medulla in embryonic life, are circumstances undoubtedly of great significance. The presence of this layer is believed to be responsible

[6] NICHOLSON, W. M.: Bull. Johns Hopkins Hosp., 1936, lviii, 405.

[7] WALTERS, W., WILDER, R. M., and KEPLER, E. J.: Suprarenal cortical syndrome with presentation of 10 cases, Ann. Surg., 1934, c, 670–688.

[8] BROWNELL, K. A., LOCKWOOD, J. E., and HARTMAN, F. A.: Lactation hormone of adrenal cortex, Proc. Soc. Exper. Biol. and Med., 1933, xxx, 783–784.

for the relatively great size of the fetal adrenal. At one period of gestation it equals the kidney in size, and at birth it is still one-third the size of the latter organ.[9]

Much of the accessory cortical tissue, particularly that in association with the reproductive organs, may well be a part of this tissue, a glandular entity, quite distinct in function from the rest of the cortex. Its involution normally begins soon after birth and is nearly complete at the end of the first year. A thin juxta-medullary zone of pigmented cells is said to persist in the adult and may be a remnant of this involuted tissue. Hypertrophy or persistence of portions of it which have not undergone involution, according to one theory, may be responsible for the adreno-genital syndrome associated with tumors of the cortex. Broster and Vines [10] report the occurrence of bright red granules, upon staining with Ponceau-Fuchsin, in the cytoplasm of adrenal cells of the reticular layer in such tumors, and find that they are also normally present in the "X" layer of embryonic life. If confirmed, such a finding would point to the undue persistence of cells from this layer into later life as one causal factor in the production of these conditions of sex reversal and stimulation. Others, however, have not been so fortunate in the demonstration of this staining reaction, and its regular occurrence in these cases is as yet not certain.

This recent evidence for the occurrence of two types of adrenal cortical tissue, quite different in their physiological significance, constitutes a new and probably an important advance in our progress toward a final solution of the problem of adrenal function.

[9] GROLLMAN, A.: The adrenals, 1936, Williams and Wilkins, Baltimore.
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REVIEWS

Textbook of Psychiatry. By ARTHUR P. NOYES, M.D. Second Edition. 329 pages; 15 × 22 cm. Macmillan Co., New York. 1936. Price, $2.50.

Dr. Noyes offers a revised edition of his popular textbook which found such wide acceptance when first issued in 1927.

It is primarily intended for nurses, but presents one of the best, simple, understandable expositions of mental mechanisms and psychiatric reaction types that we know. It is in no sense exhaustive. It is designed to give the nurse some idea of what mental disease is and a brief picture of the symptoms occurring in various types of mental reaction.

The first nine chapters are devoted to dynamics of normal and abnormal behavior and to explanation of accepted American theories as to the causes underlying emotional disorders. Most of the rest of the book devotes itself to description of clinical pictures as typically found. At the end of each clinical picture there is a short section called "Nursing Management" which gives practical suggestions as to things which the nurse can actually do to protect and help her patient. At the end of the book there is a good chapter called "Psychiatric Nursing" and a brief survey of the author's views on psychoanalysis and mental hygiene. The book ends with a fairly complete glossary of the commoner psychiatric terms.

The whole volume is clear, conservative and should be very useful to medical students or to busy general practitioners who want some concrete suggestions as to how to handle their patients. Nowhere are there any attempts to explain psychotherapy, since this, of course, does not fall within the nurse's province, but for everything else we can recommend the book.

H. M.

The Parathyroids in Health and in Disease. By DAVID H. SHELLING, B.Sc., M.D. 335 pages; 17 × 25 cm.; illustrated. C. V. Mosby Company, St. Louis. 1935. Price, $5.00.

This excellent book should prove quite valuable to special workers as well as to teachers and to those physicians and students who arrange for themselves the time to read authoritative monographs on special subjects.

The author is an acknowledged authority in the field of research on the parathyroids both experimental and clinical. His style is clear and concise. He has arranged the subject matter of the book into ten chapters dealing with the history, the anatomy, the pathology, the physiology of the parathyroids, the parathyroid hormone, tetany and hypoparathyroidism, hyperparathyroidism and osteitis fibrosa, the relation of the parathyroids to the other glands of internal secretion, the relation of the parathyroids to vitamin D, and the use and misuse of parathyroid hormone and of parathyroidectomy.

Numerous references in the text are made to the very full bibliography at the end of each chapter. It would seem to the reviewer that the world literature on the subject has been completely covered and listed.

The general excellence of the book is enhanced by the attractive format of the volume, of convenient size, excellent paper and print with many side headings in heavy black type.

T. P. S.

Cardiac Output and Arterial Hypertension. By SIDNEY A. GLADSTONE, M.D. 56 pages; 16 × 23.5 cm. 1935. Price, $1.00.

This small volume contains four papers, the first two dealing with the foreign gas methods of determining cardiac output, the third with the cardiac output in hypertension and the fourth presents an hypothesis concerning the mechanism of renal hypertension.

In the first two papers the author offers criticisms of the existing methods of determining cardiac output and presents his own modification of the acetylene method. In the third paper, using his modification of the acetylene procedure, he presents evidence that the increased work of the heart in cases of essential hypertension is due to increased peripheral resistance and not to an increased cardiac output. The fourth paper is speculative in nature, and presents no experimental work of the author in support of his conclusions.

W. S. L., JR.

Roentgenographic Technique; A Manual for Physicians, Students and Technicians. By DARMON ARTELLE RHINEGART, A.M., M.D., F.A.C.R., Professor of Roentgenology and Applied Anatomy, School of Medicine, University of Arkansas; Roentgenologist to St. Vincent's Infirmary, Baptist State Hospital, Missouri Pacific Hospital and the Arkansas Children's Hospital, Little Rock, Arkansas. Second Edition. 431 pages; 16 × 24 cm.; 183 engravings. Lea and Febiger, Philadelphia. 1936. Price, $5.50.

This is a thorough and successful attempt to present for physicians, students and technicians a text of time-tested roentgenographic technic as well as modern advances. Salient features of the volume are simplicity and comprehensiveness. The principles are presented in an orderly and logical fashion with emphasis on seemingly insignificant details of roentgenographic technic which make for thorough roentgenographic work. The sections on electricity and roentgen-ray machines and their accessories appear to be adequate to furnish the ground work for intelligent understanding of the principles.

A series of experiments is incorporated which should furnish invaluable information concerning operating characteristics of roentgen-ray machines, the laws of roentgen-ray exposure, and patient-tube-film relationship, so that the best films will be obtained. A technic based on thickness and radiographic density is advocated, a sound and universal method for obtaining consistently good roentgenograms. Sections on the radiographic peculiarities of the various parts of the body are included. The many methods of examining the various parts are mentioned, the best being more fully considered. The book should prove useful to any physician who desires a comprehensive knowledge of radiographic technic.

H. J. W.

Evaluation of Symptoms. By OLIVER T. OSBORNE, M.D. 163 pages; 14 × 21 cm. Yale University Press, New Haven, Connecticut. 1935. Price, $3.50.

The author has written a small book in which he summarizes in seven chapters points which his long experience has shown him to be of particular value to the practising physician. He discusses history taking, examination, principles of therapy, certain specific diseases and then takes up symptoms separately in alphabetic order. There is a great deal of information in small compass.

M. C. P.

COLLEGE NEWS NOTES

Gifts to the College Library

Acknowledgment is made of the receipt of the following gifts to the College Library of publications by members:

Dr. Wm. W. Cadbury (Fellow), Moorestown, N. J., on leave of absence from Canton, China—1 autographed book, "At the Point of a Lancet";
Dr. Logan Clendening (Fellow), Kansas City, Mo.—1 book, "The Balanced Diet";
Dr. R. Manning Clarke (Fellow), Los Angeles, Calif.—1 reprint;
Dr. Albert Soiland (Fellow), Los Angeles, Calif.—2 reprints;
Dr. William E. Costolow (Fellow), Los Angeles, Calif.—1 reprint;
Dr. Isidore Lattman (Associate), Washington, D. C.—3 reprints.
Dr. G. Philip Grabfield (Fellow), Boston, Mass.—18 reprints;
Dr. Samuel J. McClendon (Fellow), San Diego, Calif.—2 reprints;
Dr. Oliver T. Osborne (Fellow), New Haven, Conn.—1 reprint;
Dr. L. B. Carruthers (Associate), Miraj, India—2 reprints;
Dr. William C. Cooke (Associate), San Diego, Calif.—2 reprints;
Dr. Warren W. Quillian (Associate), Coral Gables, Fla.—4 reprints;
Dr. Joseph B. Wolffe (Associate), Philadelphia, Pa.—2 reprints.

The Washington School of Psychiatry

Early in 1933, the Training Committee of The Washington-Baltimore Psychoanalytic Society began a formal schedule of didactic lectures and seminars in keeping with the tradition of branch societies of The International Psychoanalytical Association. These training courses have been continued regularly from the beginning. The Committee incorporated the William Alanson White Psychoanalytic Foundation, having in view a psychoanalytic institute similar to that maintained in other training centers. However, experience of teaching and training dictated the need for postgraduate work in every field of interest to the psychiatrist. This led to plans for a school that would represent most truly American psychiatry and which would be unlimited in its scope. The outgrowth has been the incorporation of The Washington School of Psychiatry, with Dr. White as its Honorary President. Among its officers, in addition to Dr. White, who is a Fellow of the American College of Physicians, are the following:

Dr. Harry Stack Sullivan, President and Chairman of the Faculty
Dr. Lucile Dooley, Vice-President
Dr. Ross McClure Chapman (Fellow), Vice-President and Provost
Dr. William K. Ryan, Treasurer
Dr. Ernest E. Hadley (Associate), Secretary and Executive Director
Dr. Joseph L. Gilbert (Fellow), Registrar

State Meeting—Illinois Members

The second annual meeting of the members of the American College of Physicians of the State of Illinois, outside of Chicago, was held September 24, 1936, at Peoria. The meeting was called by Dr. Samuel E. Munson, of Springfield, Governor for Southern Illinois, and the invitations were sent by Dr. George Parker, of Peoria.

The meeting was held at the Creve Couer Club, and opened at four o'clock with the following guest speakers:

Dr. Allen K. Krause (Fellow), Baltimore, Md.—"Future Possibilities of the Diagnosis of Tuberculosis";

Dr. Horace W. Soper (Fellow), St. Louis, Mo.—"Clinical Significance of Milk and Cholesterol in the Dietary of Man";

Dr. Frank Smithies (Master), Chicago, Ill.—"Certain Ulcerative Lesions of the Bowel, Their Recognition and Management."

Dinner was served at six-thirty, after which a short report was made by Dr. Samuel E. Munson, Governor for Southern Illinois, who spoke in regard to the work of the committee that had been appointed about two years ago to act in connection with the Section on the Practice of Medicine of the American Medical Association to form an American Board for the purpose of establishing rules for the qualification of candidates and conducting examinations. This was accomplished in June of this year, with such rules and regulations as will govern its requirements for certification of those desiring to become internists. He also spoke of the officers of the College having acquired a suitable and permanent home for the College in Philadelphia. In addition to other requirements available, conference rooms may be used by members of the College as headquarters when in Philadelphia.

Dr. Munson stated that inasmuch as the meeting at Springfield last year so unanimously met with approval, it was decided to accept the invitation of the Peoria Fellows and meet with them this year. It was agreed that no mistake was made in accepting this invitation, as we had ample proof of their cordiality and hospitality as good fellows upon this occasion.

When the call for this meeting reached the members through Dr. George Parker, and the names of those who were to address the meeting were read, a thrill of pleasure and appreciation was felt that these distinguished Fellows were to be our guests and speakers. Not only were we honored by their presence as guests, but as clinicians and writers whose names are well known as authorities in their respective fields of medicine.

One of our guests whose name for many years has been synonymous with the most advanced thought in the diagnosis and treatment of tuberculosis, Editor of the *American Review of Tuberculosis,* was Dr. Allen K. Krause, of Baltimore.

Another whose name has been no less widely known as a teacher and author in the field of diseases of digestion was Dr. Horace W. Soper, of the Soper-Mills Clinic, St. Louis.

Our third speaker, Secretary-General of the College from 1922 to 1926, and later its President, and the only one in Illinois who has been honored by being made a Master of the College, now Editor of the *American Journal of Digestive Diseases and Nutrition,* was Dr. Frank Smithies, of Chicago.

In their letters of acceptance, each of these men expressed the appreciation and honor they felt in receiving an invitation to address the Fellows of the College from Illinois.

The following members of the College were present: Thomas A. Starkey, of Beardstown; Gerald M. Cline, Henry W. Grote, Edgar M. Stevenson, of Bloomington; D. O. N. Lindberg, Perry J. Melnick, of Decatur; James C. Redington, of Galesburg; Albert H. Dollear, Warner H. Newcomb, of Jacksonville; Orville Barbour, Harry A. Durkin, Fred M. Meixner, George Parker, Maxim Pollak, John R. Vonachen, of Peoria; Warren F. Pearce, Hildegarde C. Germann Sinnock, Harold Swanberg, of Quincy; Major Eugen G. Reinartz, of Chanute Field, Rantoul; Samuel E. Munson, Thomas D. Masters, Emmet F. Pearson, George B. Stericker, of Springfield; Villairs T. Austin, Charles H. Drenckhahn, of Urbana.

There were also present about fifteen guests, invited by the Peoria Fellows, and Dr. R. L. Green, of Peoria, President of the Illinois State Medical Society.

Special Meeting, Board of Regents

A meeting of the Board of Regents of the American College of Physicians has been called by the President, Dr. Ernest B. Bradley, at the College Headquarters in Philadelphia on December 13, 1936. Various committees of the College will meet December 12, as will also the American Board of Internal Medicine. About two hundred and fifty candidates for Associateship or Fellowship are to be considered, and much other important College business will be transacted. The Committee on Constitution and By-Laws will present suggested amendments to the by-laws governing the admission of future candidates to Fellowship. The Committee on Future Policy for the Development of Internal Medicine may also present to the Regents recommendations for additional activities of the College in the future.

The New York Post-Graduate Medical School and Hospital conducted a Symposium on Dysentery, September 26, 1936. Among those presenting papers were Dr. George W. McCoy (Fellow), Director of the National Institute of Health, Washington, D. C., "Relationship of the Problem of Dysentery to the U. S. Public Health Service"; Dr. Ward J. MacNeal (Fellow), Professor of Pathology and Bacteriology, New York Post-Graduate Medical School, "Bacteriophages in the Treatment of Intestinal Disease"; Dr. Z. Bercovitz (Associate), Instructor in Medicine, New York Post-Graduate Medical School, "Methods for Differential Diagnosis in Dysentery." Dr. Walter G. Lough (Fellow), Executive Officer, Department of Medicine, New York Post-Graduate Medical School, acted as Chairman of that part of the program dealing with "Dysentery and the Clinician."

Dr. D. O. N. Lindberg (Fellow), Decatur, Ill., has been elected President of the Mississippi Valley Sanatorium Association.

Dr. G. Harlan Wells (Fellow), Philadelphia, was elected President of the Homeopathic Medical Society of Pennsylvania on September 23, 1936. Dr. E. Roland Snader (Fellow), Philadelphia, was elected a trustee and Dr. E. W. Stitzel (Fellow), Altoona, was elected censor.

Dr. Frank S. Horvath (Associate), Washington, D. C., has been appointed Associate Professor of Clinical Medicine at Georgetown University School of Medicine.

Dr. W. D. Weis (Fellow), County Health Commissioner for Lake County, Ind., brought more forcibly to the residents of that County the matter of health and sanitation by having a Health and Sanitation Exhibit at the Lake County Fair during the past autumn. Exhibits and demonstrations were arranged under Dr. Weis' direction by the Northwest Indiana Dental Society, the Lake County Tuberculosis Sanatorium, the Lake County Tuberculosis Association, the Weights and Measures Division of the Indiana Department of Public Health, the League for the Hard of Hearing, the Health Department of the City of Hammond, the Milk and Dairy Division of the Indiana Department of Public Health, the Lake County Safety Council, the Lake County Health Department and other agencies. Resort was made to motion pictures, charts, maps and various other means by which the interest of the citizens would be aroused and a proper impression of the importance of health measures carried to the homes throughout the County.

The Mississippi Valley Medical Society, being the Tri-State Post Graduate Assembly of Illinois, Missouri and Iowa, held its second annual meeting at Burlington, Iowa, September 30 to October 2. Among the guest speakers was Dr. Ralph Kinsella

(Fellow), St. Louis, Mo., representing Internal Medicine. Dr. Willard O. Thompson (Fellow), Chicago, Ill., and Dr. Leon Unger (Associate), Chicago, Ill., presented scientific exhibits on "Glands of Internal Secretion" and "Allergy," respectively. Among the clinical lecturers were Dr. James G. Carr (Fellow), Chicago, Ill.; Dr. Charles A. Elliott (Fellow), Chicago, Ill.; Dr. F. H. Lamb (Associate), Davenport, Iowa; Dr. Frank P. McNamara (Fellow), Dubuque, Iowa; Dr. Joseph L. Miller (Fellow), Chicago, Ill.; Dr. Warren Pearce (Fellow), Quincy, Ill.; Dr. John H. Peck (Fellow), Des Moines, Iowa; Dr. J. C. Redington (Associate), Galesburg, Ill.; Dr. Howard Rusk (Fellow), St. Louis, Mo.; Dr. Leon Unger (Associate), Chicago, Ill.; and Dr. Italo F. Volini (Fellow), Chicago, Ill.

Among the officers of the Society were Dr. D. G. Stine (Fellow), Columbia, Mo., First Vice-President; Dr. J. I. Marker (Fellow), Davenport, Iowa, Third Vice-President; and Dr. Harold Swanberg (Fellow), Quincy, Ill., Secretary-Treasurer. Dr. G. M. Cline (Fellow), Bloomington, Ill., Dr. Harold Swanberg (Fellow), Quincy, Ill., and Dr. E. S. Smith (Fellow), Kirksville, Mo., are members of the Board of Directors.

Dr. Maximilian J. Hubeny (Fellow), Chicago, has been made chief of the X-Ray Department of Cook County Hospital.

Dr. George B. Eusterman (Fellow), Rochester, Minn., Dr. Alan Brown (Fellow), Toronto, Ont., and Dr. Elliott P. Joslin (Fellow), Boston, Mass., were among the guest speakers on the program of the Omaha Mid-West Clinical Society, held at Omaha, October 26 to 30.

Dr. James J. McGuire (Fellow), Trenton, has been elected Secretary of the New Jersey State Board of Medical Examiners.

Recent promotions on the Faculty of the College of Physicians and Surgeons of Columbia University include the following:

Dr. J. Burns Amberson, Jr. (Fellow), Professor of Clinical Medicine
Dr. Robert L. Levy (Fellow), Professor of Clinical Medicine
Dr. Alvan L. Barach (Fellow), Assistant Professor of Clinical Medicine
Dr. Charles A. McKendree (Fellow), Clinical Professor of Neurology

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Dr. Clarence M. Grigsby (Fellow and former Governor for Texas), Professor of Clinical Medicine at Baylor University College of Medicine, Dallas, was guest of honor at a recent dinner celebrating his completion of twenty-five years as a member of the faculty of that institution.

Dr. Ramon M. Suarez (Fellow and Governor for Puerto Rico) addressed the first scientific meeting of the Puerto Rico chapter of the Pan American Medical Association in San Juan recently, on "The Study of the Bone Marrow in Chronic Schistosomiasis Mansoni."

Sir Frederick Banting (Fellow) and Dr. Charles H. Best, both of the University of Toronto Faculty of Medicine, and Dr. James B. Collip (Fellow), McGill University Faculty of Medicine, Montreal, were the recipients of the Frederick Newton Gisborne Starr Medal awarded at the last meeting of the Canadian Medical Association "for preëminent services to the cause of medicine in Canada." The Starr Medal was established in 1935 by the widow of the late Dr. Starr, who for several years was the General Secretary of the Association, and President in 1927.

Among the guest speakers at the annual meeting of the Indiana State Medical Association at South Bend, October 6 to 8, were the following Fellows of the College:

Dr. Byrl R. Kirklin, Rochester, Minn.
Dr. Russell L. Cecil, New York City
Dr. Francis E. Senear, Chicago, Ill.
Dr. Elmer L. Sevringhaus, Madison, Wis.
Dr. John A. Toomey, Cleveland, Ohio

Dr. Hugo A. Freund (Fellow), Detroit, President of the Children's Fund of Michigan, presented a symposium on "What Constitutes a Complete Health Service for the Community?" at a conference between the University of Michigan and the Fund, at Marquette, recently. Dr. Arthur C. Curtis (Fellow), Ann Arbor, delivered an address on "Etiology and Management of Chronic Arthritis."

The following Fellows of the American College of Physicians addressed the Fourteenth Annual Conference of the Kansas City Southwest Clinical Society at Kansas City, October 4 to 8:

Dr. Milton A. Bridges, New York City
Dr. Joseph A. Capps, Chicago, Ill.
Dr. J. Arthur Myers, Minneapolis, Minn.

Dr. Morris Maslon (Fellow), Glens Falls, N. Y., was a guest of honor at a testimonial dinner at the Fort William Henry Hotel, Lake George, recently, celebrating his twenty-fifth anniversary as head of the Warren County Laboratory.

Dr. Coy C. Carpenter (Fellow), who has been acting dean of Wake Forest College of Medicine, Wake Forest, N. C., has now been elected dean to succeed Dr. Thurman D. Kitchin (Fellow), who was made president of the College in 1930.

Dr. Edward S. King (Associate), Professor of Physiologic Chemistry and Bacteriology, is on leave of absence, spending the present term at Harvard University Medical School, Boston.

The first "Harlow Brooks Memorial Navajo Clinical Conference" was held August 31 to September 1 at Ganado, Ariz. Among the speakers was Dr. Milo K. Tedstrom (Fellow) of Santa Ana, Calif. The conference will be held annually and is named in honor of the late Dr. Harlow Brooks (Fellow), New York City, who was interested in the work of the Sage Memorial Hospital at Ganado, which is in the heart of the Navajo reservation. Dr. Brooks was an authority on Indian practices and customs.

The Iowa State Medical Society has been offering graduate courses in various Iowa cities during the present autumn. Dr. Arthur U. Desjardins (Fellow), Rochester, Minn., gave a lecture on "Evaluation of Radiologic Diagnosis and Treatment of Cancer"; Dr. Samuel A. Levine (Fellow), Boston, "Modern Cardiac Therapy"; Dr. William S. Middleton (Fellow), Madison, Wis., "The Barbiturates in the Treatment of Disease"; Dr. Paul A. O'Leary (Fellow), Rochester, Minn., "Treatment of Syphilis"; Dr. Philip S. Hench (Fellow), Rochester, Minn., "Diagnosis and Treatment of Arthritis"; Dr. Maurice C. Howard (Fellow), Omaha,

Nebr., "Diagnosis and Treatment of the Anemias"; Dr. Byrl R. Kirklin (Fellow), Rochester, Minn., "Roentgenologic Diagnosis"; and Dr. Russell M. Wilder (Fellow), Rochester, Minn., "Modern Treatment of Diabetes."

Dr. John Harvey (Fellow), Lexington, Ky., delivered the annual oration in medicine of the Kentucky State Medical Association at Paducah on October 6, his subject being "Our Duty to the Art and Science of Medicine."

Dr. George Herrmann (Fellow), Galveston, Tex., addressed the seventy-first annual meeting of the Michigan State Medical Society, September 21 to 24, on "Further Studies of the Mechanism of Action and of the Relative Effectiveness of the Newer Diuretics."

The Ohio State Medical Association held its ninetieth annual meeting in Cleveland, October 7 to 9, under the presidency of Dr. Ralph R. Hendershott (Associate), Tiffin, Ohio.

Dr. Samuel A. Levine (Fellow), Boston, assistant professor of medicine, Harvard University Medical School, delivered a lecture on "Diseases of the Heart and Allied Pathologic Conditions" in connection with the graduate lectures sponsored by the Lima and Allen County (Ohio) Academy of Medicine during September.

The Medical Society of Milwaukee County, Wisconsin, sponsored a course of graduate lectures on syphilis given at Marquette University School of Medicine, Milwaukee, recently. Among the lecturers and their subjects were:

Dr. Udo J. Wile (Fellow), Ann Arbor, Mich., "Bone, Joint and Visceral Syphilis"; Dr. James E. Paullin (Fellow), Atlanta, Ga., "Public Health Aspects of Syphilis"; and Dr. Paul A. O'Leary (Fellow), Rochester, Minn., "Treatment of Syphilis."

Col. Henry C. Pillsbury (Fellow), Medical Corps, U. S. Army, has been assigned to duty as chief health officer of the Panama Canal Zone.

Dr. Frank H. Krusen (Associate), Rochester, Minn., and Dr. William J. Egan (Fellow), Milwaukee, Wis., have been elected vice-presidents of the American Congress of Physical Therapy for the coming year.

Dr. Ernest B. Bradley (Fellow and President) addressed the Jefferson and Fayette County Medical Societies at Louisville, Ky., September 21, on "A Medical Glance at the Past Thirty Years."

Dr. George W. McCoy (Fellow), Director of the National Institute of Health, Washington, D. C., was one of the speakers on the occasion of the dedication of the new public health laboratory of the New York City Department of Health, named in honor of Dr. William Hallock Park, founder and director emeritus of the laboratory.

Dr. William S. McCann (Fellow), Rochester, N. Y., and Dr. Elliott P. Joslin (Fellow), Boston, Mass., were guest speakers at the eighty-sixth annual meeting of the Medical Society of the State of Pennsylvania, held in Pittsburgh October 5 to 8.

Dr. Kenneth M. Lynch (Fellow) and Dr. Joseph H. Cannon (Fellow), both of Charleston, S. C., and Dr. James E. Paullin (Fellow), Atlanta, Ga., delivered lectures on diseases of the kidney at the second annual clinical assembly presented by the Anderson County (South Carolina) Medical Society, September 8 to 10.

Dr. Edgar A. Hines (Fellow), Seneca, S. C., was president of the assembly.

Dr. John A. Kolmer (Fellow), Philadelphia, and Dr. Josephine B. Neal (Fellow), New York City, conducted a panel discussion on poliomyelitis in connection with the fourth annual fall clinical session of the Maine Medical Association, held at Waterville, Maine, October 15 to 16.

Dr. Paul Dudley White (Fellow), assistant professor of medicine, Harvard Medical School, delivered the principal address on the occasion of Ether Day at the Massachusetts General Hospital, October 16.

The New York Academy of Medicine presented its ninth annual graduate fortnight, October 19 to 31, on "Trauma, Occupational Diseases and Hazards." Among the speakers and their subjects were:

Major Samuel A. White (Fellow), Medical Corps, U. S. Army, "Medical Aspects of Chemical Warfare"; Dr. Elliott P. Joslin (Fellow), Boston, "Relation of Trauma to Diabetes"; and Dr. J. Burns Amberson, Jr. (Fellow), New York City, "Pulmonary Disease."

The late Dr. James M. Anders (Master), Philadelphia, who died August 29, provided in his will after the death of his widow $50,000 for the establishment of the James M. Anders Foundation in the Graduate School of Medicine of the University of Pennsylvania; $2,500 to the Philadelphia County Medical Society to defray the expenses of the annual "Public Health Day" in the public schools; $2,000 for the endowment fund of the Society's library, and further provided that the library committee of the Philadelphia County Medical Society may select such books from his library as they choose.

Dr. Julius H. Hess (Fellow), Chicago, and Dr. John A. Toomey (Fellow), Cleveland, will be guest speakers at the fourth annual meeting in Atlanta of the Georgia Pediatric Society, December 10.

Dr. Wyndham B. Blanton (Fellow), professor of the history of medicine, Medical College of Virginia, has been appointed one of the editors of the "Annals of Medical History."

The seventh annual fall clinical conference of the Oklahoma City Clinical Society was held October 26 to 29. Among the speakers and their titles were the following:

Dr. Wilburt C. Davison (Fellow), Dean of the School of Medicine and Professor of Pediatrics, Duke University, Durham, N. C.—Pediatrics;

Dr. Charles L. Brown (Fellow), Professor of Medicine and Head of the Department of Medicine, Temple University School of Medicine, Philadelphia —Internal Medicine;

Dr. F. E. Senear (Fellow), Professor and Head of the Department of Dermatology, University of Illinois College of Medicine, Chicago—Dermatology;
Dr. Hans Lisser (Fellow), Clinical Professor of Medicine, University of California Medical School, Berkeley-San Francisco—Endocrinology.

Dr. F. O. Mahony (Fellow), El Dorado, Ark., has been appointed vice-president of the State Board of Health.

Dr. Paul Brindley (Fellow), Galveston, and Dr. May Owen (Fellow), Fort Worth, have been elected president and vice-president respectively of the Texas State Pathological Society.

Dr. Alex. F. Robertson, Jr. (Fellow), Staunton, Va., has been elected secretary of the Augusta County (Virginia) Medical Society.

Honoring the sixty-seventh birthday of Dr. Francis M. Pottenger (Fellow and ex-President), a large number of patients and former patients joined members of Dr. Pottenger's family and the Staff of the Sanatorium in an informal reception given for him on Sunday afternoon, September 27, in the beautiful gardens of the Pottenger Sanatorium at Monrovia, Calif. There were about two hundred guests present, among whom were patients who left the Sanatorium as far back as 1905.

Dr. Pottenger received many beautiful gifts from associates and patients, and congratulatory telegrams from patients and friends unable to attend. A buffet supper was served in the gardens.

Major James Stevens Simmons (Fellow), Medical Corps, U. S. Army, who in 1934 organized the Army Medical Research Board, Ancon, Canal Zone, and who during the past two years has been engaged in an investigation of malaria and its anopheline vectors in Panama, has been transferred for duty as Assistant to the Corps Area Surgeon, Headquarters First Corps Area, Army Base, Boston, Mass.

Dr. Chester North Frazier (Fellow), Professor of Dermatology and Syphilology, Peiping Union Medical College, Peiping, China, is on furlough and is engaged in studying biostatistics in the School of Hygiene and Public Health of the Johns Hopkins University, Baltimore.

Dr. Paul P. McCain (Fellow), Medical Director of the North Carolina Sanatorium for the Treatment of Tuberculosis, has been awarded the degree of LL.D. by the University of North Carolina.

Dr. Perry J. Melnick (Associate), Dectur, Ill., received the degree of Doctor of Philosophy in Pathology from the University of Illinois College of Medicine last June.

Dr. Allen K. Krause (Fellow), Director of the Desert Sanatorium, Tucson, Ariz., is on leave of absence and is now in Baltimore, Md., where he was formerly Associate Professor of Medicine on the faculty of Johns Hopkins University. Dr. Krause still retains the title of Lecturer in Medicine at Johns Hopkins University School of Medicine, and is a "Fellow by Courtesy in Epidemiology" in the Johns Hopkins School of Hygiene. He is Editor of the "American Review of Tuberculosis," and during the coming year will devote his time to study and writing.

OBITUARIES

DR. WILLIAM H. MAYER

In the death of Dr. William H. Mayer (Fellow) on August 22, 1936, from septic pneumonia, organized medicine lost one of its most loyal supporters, one who in spite of almost unsupportable physical handicap had been unsparing of time and energy in his devotion to the affairs of his county and state societies and of the American Medical Association.

Dr. Mayer was born in Pittsburgh, Pa., October 30, 1887, the son of William L. and Anna Bickman Mayer.

He received his preliminary education in Pittsburgh Central High School, and after graduating from the University of Pennsylvania Medical School in 1912, served his internship in Mercy Hospital, Pittsburgh. Entering into practice he devoted himself to the field of neurology and psychiatry. Dr. Mayer was Neurologist to Allegheny General Hospital and Passavant Hospital, Associate Psychiatrist to St. Francis Hospital, Assistant Professor of Neurology in the School of Medicine of the University of Pittsburgh. In addition to membership in the County and State societies he was a Fellow of the American Medical Association, the Pittsburgh Academy of Medicine and the American College of Physicians. He was a member, also, of the American Psychiatric Association and of the Association for Research in Mental and Nervous Diseases.

Dr. Mayer served as secretary of the Allegheny County Medical Society from 1917 to 1925, in which year he became President-Elect of the Medical Society of the State of Pennsylvania.

He also served his county society, as a member of the Board of Directors, chairman of the Finance Committee, and as elected delegate to the State Society. In 1931 he was installed as President of the Medical Society of the State of Pennsylvania. Consecutively, since 1921 he was chosen to succeed himself as delegate from his State Society to the House of Delegates of the American Medical Association.

Dr. Mayer was twice married; his first wife was Miss Emma J. Glass of London, Ontario, who died several years ago. He later married Miss Virginia Diehl Sutton of Pittsburgh, who with their baby daughter, Ann Virginia, born February 29, 1936, survives him.

E. Bosworth McCready, M.D., F.A.C.P.,
Governor for Western Pennsylvania

DR. HOWARD E. MARCHBANKS

Dr. Howard E. Marchbanks (Fellow), of Pittsburg, Kansas, died August 7, 1936, of coronary occlusion.

Dr. Marchbanks was born in Scammon, Kansas, July 18, 1888. He graduated from Cherokee High School, entered the University of Kansas

and received his A.B. He then entered the University of Kansas Medical School and graduated in 1916. He served his internship at the Bell Memorial Hospital in Kansas City, Kansas.

He was a member of the Phi Beta Pi Medical Fraternity. During the World War he served as First Lieutenant in the Medical Corps attached to the 218th Engineers. He received his discharge from the service February 4, 1919.

In 1919 Dr. Marchbanks took postgraduate work under Dr. Richard Cabot in the Harvard Medical School at Boston. He was a member of the American Medical Association, The Kansas Medical Society, The Southeast Kansas Medical Society, The Jackson County (Missouri) Medical Society. He was one of the associate editors of the Journal of the Kansas Medical Society. In 1931 Dr. Marchbanks was made a Fellow of the American College of Physicians.

THOMAS T. HOLT, M.D., F.A.C.P.,
Governor for Kansas